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Draft
Guidelines for the Prevention of Opportunistic Infections (OIs) in Bone Marrow Transplant (BMT) Recipients

To ensure consideration for inclusion in the final version of this document, written comments must be received on or before November 1, 1999, the end of the 45-day public comment period. Comments should be sent to Clare A. Dykewicz, M.D., M.P.H., Division of AIDS, STD, and TB Laboratory Research, National Center for Infectious Diseases, Mailstop A-12, Centers for Disease Control and Prevention, 1600 Clifton Rd., N.E., Atlanta, GA 30333; telephone (404) 639-4932; FAX (404) 639-4664; E-mail: <cad3@cdc.gov>.

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INTRODUCTION AND BACKGROUND

Introduction

In 1992, the Institute of Medicine (IOM) published a report entitled *Emerging Infections: Microbial Threats to Health in the United States* (1). In this report, IOM recommended that the Centers for Disease Control and Prevention (CDC) lead a national and global effort to detect and control emerging infectious agents. In response to this recommendation, CDC published *Addressing Emerging Disease Threats: A Strategy for the United States* (2). This plan outlined national disease prevention priorities, including the development of guidelines for preventing opportunistic infections (OIs) in immunosuppressed persons.

CDC published guidelines for preventing OIs in persons infected with human immunodeficiency virus (HIV) in 1995 as well as a revised editions in 1997 and 1999 (3, 4, 5). Because of the success of these guidelines, CDC sought to determine the need for expanding OI prevention activities to include other immunosuppressed populations. Findings from an informal survey of hematology, oncology, and infectious disease specialists at transplant centers and from a working group (Table 1) formed by CDC to examine these issues indicated that guidelines were needed to help prevent OIs in bone marrow transplant (BMT) recipients.

The working group defined OIs as infections which occur with increased frequency or severity in BMT recipients, and proceeded to draft evidence-based recommendations to prevent exposure to bacterial, fungal, viral, protozoal, and helminthic pathogens, as well as recommendations to prevent diseases when exposure occurs. Sections on hospital infection control and BMT safety were also developed. Unless specifically stated, recommendations address both allogeneic and autologous BMT recipients. Specific notes for autologous *vs*. allogeneic transplant recipients and pediatric patients were included. The guidelines were developed for BMT recipients, their household and close contacts, transplant and infectious diseases specialists, BMT unit and clinic staff, and public health professionals.

In March 1997, the working group presented the first draft of the guidelines at a meeting of representatives from public and private health organizations (Table 2) held at CDC in Atlanta. Among the many comments received from the meeting participants was that an immunization schedule should be developed for BMT recipients.

Despite or rather because of the lack of published guidelines for reimmunization of BMT recipients, BMT centers have developed a range of individual immunization cocktails for BMT recipients (5a). Henning, *et al*. found at least half of the surveyed programs routinely immunized BMT recipients for diphtheria, tetanus, polio, Hemophilus influenzae type b (Hib), measles-mumps-rubella, Hepatitis B, pneumococcus and influenza (5a). Of programs that had BMT recipients <7 years of age, only 26% and 34% routinely administered 2 or more doses of diphtheria-tetanus-pertussis (DTP) and inactivated polio vaccine (IPV) respectively to their BMT recipients (5a). Of programs with BMT recipients ≥7 years of age, only 32% and 31% routinely administered 2 or more doses of tetanus-diphtheria (Td) and IPV respectively to their BMT recipients (5a). For programs with BMT recipients <7 years of age, the number of immunization schedules ranged from 3-10 schedules per vaccine. For programs with BMT recipients at least 7 years of age, 3-11 schedules were used per vaccine (5a). Therefore, the study indicated that vaccines are inconsistently used and underutilized post-BMT despite convincing evidence of decline in titers post-BMT (5a). Henning, *et al*. called for national guidelines for doses and timing of vaccines post-BMT to ease confusion among BMT centers about how to vaccinate their patients (5a).

To address this need, an interim immunization schedule for BMT recipients was drafted in collaboration with several organizations (Table 3), including CDC's Advisory Committee on Immunization Practices. One goal of vaccination of BMT recipients is to routinely vaccinate them against the usual vaccine preventable diseases so that they can catch up to the level of vaccine preventable disease immunity in the non-BMT population. Another goal is to immunize them against diseases which are likely to cause increased morbidity and mortality because of their immunocompromised state, (e.g., influenza and pneumococcus).

The purpose of issuing a vaccination schedule now is to provide some guidance for BMT centers, while waiting for further studies on vaccine immunogenicity and efficacy in BMT recipients. Where no specific trials have been performed in hematopoietic transplant recipients, recommendations for immunization of BMT recipients are based on standard immunization recommendations for immunocompetent hosts with the important exception of avoiding live virus vaccines. The schedule of recommended vaccination is presented in table form for all

recipients of allogeneic, autologous, blood and marrow grafts. Also, immunization of family members, household contacts, and health care workers are recommended to minimize exposure of vaccine-preventable diseases to BMT recipients. Immunizations should be a standard feature of follow-up care of the BMT recipient, although specific recommendations will likely evolve as further data become available. The immunization schedule is included in the guidelines. (See *Immunization* section).

For all recommendations, the recommended strategies are rated by both the strength of the recommendation as well as the quality of the evidence supporting the recommendation (Tables 4 and 5). This rating system was developed by the Infectious Disease Society of America and the U.S. Public Health Service for use in the guidelines for preventing OIs in HIV-infected persons (3-5). In Table 4, an A rating means that this is something one should always do, B is something one should generally do, C is optional, and D and E ratings refer to things one should not do, with increasing degrees of contraindication. Table 5 lists the 3 categories designated by Roman numerals used to rate the quality and type of supporting evidence for a recommendation. The rating system allows assessments of the recommendations to which adherence is most important. Following review by the attendees of the March, 1997 meeting and other experts, the guidelines are being made available on September 15, 1999 for a 45 day public comment period following publication of a notice in the Federal Register.

Background

Bone marrow transplantation is the infusion of hematopoietic stem cells from a donor into a patient who has received chemotherapy which is usually marrow ablative. During the last several decades, BMTs have been used increasingly to treat a growing number of illnesses including neoplastic diseases, hematologic disorders, immunodeficiency syndromes, congenital enzyme deficiencies, and, recently, autoimmune disorders such as systemic lupus erythematosus and multiple sclerosis (6-9). BMT is no longer considered investigational and has now become standard treatment for many conditions (6,10,11). Data from the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR) indicate that approximately 15,000 blood and marrow transplants were performed in

North America in 1996, a three-fold increase over the number performed in 1989.

In these guidelines, BMT is defined as any transplantation of hematopoietic cells, regardless of transplant type (allogeneic *vs*. autologous) or cell source (bone marrow, peripheral blood, or placental/umbilical cord blood). BMTs are classified as either allogeneic or autologous depending on the source of the transplanted hematopoietic progenitor cells. Cells used in allogeneic BMTs are harvested from a donor other than the transplant recipient; such transplants are the most effective treatment for persons with severe aplastic anemia (12) and offer the only curative therapy for persons with chronic myelogenous leukemia (11). Also, for the purposes of these guidelines, BMT recipients are presumed "immunocompetent" if they are $\geq$24 months post-BMT, are not on immunosuppressive therapy, and do not have graft-versus-host disease (GVHD).

Allogeneic transplants are usually most successful when the donor is an HLA-identical twin or matched sibling. However, for the majority of allogeneic BMT candidates who lack such a donor, registry organizations such as the National Marrow Donor Program (NMDP) maintain computerized databases which store information on HLA type from millions of volunteer donors (14-16). Another source of stem cells for allogeneic BMT candidates without an HLA-matched sibling is a mismatched family member (20, 21). However, persons who receive allogeneic grafts from donors who are not HLA-matched siblings are at a substantially greater risk for GVHD, suboptimal graft function, and delayed immune recovery (22). In an effort to reduce GVHD in allogeneic BMT, a variety of techniques have been developed to remove T- lymphocytes, the major effectors of GVHD, from the donor graft. Although the recipients of T-lymphocyte depleted marrow grafts generally have lower rates of GVHD, they also have greater rates of graft rejection, CMV infection, invasive fungal infection, and EBV-associated post-transplant lymphoproliferative disease (22a).

In an autologous BMT, the patient's own cells are used. Also similar to autologous transplants are syngeneic transplants in which the HLA-identical twin of the candidate serves as the donor. Autologous BMTs are preferred for patients who require high level/marrow ablative chemotherapy to eradicate an underlying malignancy but have healthy, undiseased bone marrows and where the immune anti-tumor effect of an allograft is not beneficial. Autologous BMTs are

used most frequently to treat breast cancer, non-Hodgkin's lymphoma, and Hodgkin's disease (13). Autologous (or syngeneic) BMTs do not confer a risk for graft-versus-host disease (GVHD), a condition which occurs when the transplanted cells recognize the recipient's cells as non-self and attack them.

Within the last several years, some centers have begun to harvest hematopoietic progenitor cells from placental or umbilical cord blood (UCB) immediately after birth. These harvested cells are used primarily for allogeneic transplants, particularly among children. Early results suggest that greater degrees of histoincompatibility between donor and recipient might be tolerated without graft rejection or GVHD when UCB hematopoietic cells are used (17-19). Immune function after UCB transplants has not yet been well-studied.

BMT is rapidly evolving in other areas also. For example, hematopoietic progenitor cells harvested from the patient's peripheral blood following treatment with hematopoietic colony-stimulating factors such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) are being used increasingly in autologous BMT recipients (23) and are under investigation for use in allogeneic BMT. Peripheral blood has largely replaced bone marrow as a source of stem cells for autologous BMT recipients. A benefit of harvesting such cells from the donor's peripheral blood instead of bone marrow is that it eliminates the need for general anesthesia associated with bone marrow aspiration.

Although the use of intravenous immune globulin (IVIG) in the routine management of allogeneic BMT patients was common some years ago as a means of producing immune modulation in patients with GVHD, this practice has declined in an ever increasing cost containment climate (23a) and after the development of other strategies for GVHD prophylaxis (23b). For example, use of cyclosporine GVHD prophylaxis has become commonplace since its introduction in the early 1980s. Most frequently, cyclosporine is given in combination with other immunosuppressive agents such as methotrexate, corticosteroids, and/or tacrolimus (FK506) (23b). Although cyclosporine is effective in preventing GVHD, its use entails greater hazards for infectious complications (and relapse of the underlying neoplastic disease for which the transplant was performed).

Although survival rates for some autologous BMT recipients have improved (24, 25),

infection remains the leading cause of death in allogeneic BMTs from unrelated donors, and is a major cause of morbidity in other types of BMTs (25). The NMDP reported that of 462 persons receiving unrelated allogeneic BMTs from December 1987 to November 1990, 66% had died by 1991 (15). Among primary and secondary causes of death, the most common cause was infection, which occurred in 37% of 307 patients (15). Efforts to reduce the rates of infection could therefore potentially improve survival of some allogeneic BMT recipients (e.g., those with unrelated donors).

Despite high morbidity and mortality following BMT, recipients who survive long-term are likely to enjoy good health. A survey of 798 persons who had received a BMT before 1985 and had survived for more than 5 years post BMT found that 93% were in good health and that 89% had returned to work or school full time (26). In another survey of 125 adults who had survived a mean of 10 years after BMT, 88% responded that the "benefits of transplantation outweighed the side effects" (27).

Immune Recovery Post-BMT

During the first year following a BMT, recipients typically follow a predictable pattern of immune deficiency and recovery, which begins with the effects of the chemotherapy and/or radiation therapy (the conditioning regimen) given just before the BMT to treat the underlying disease. Unfortunately, this conditioning regimen also destroys normal hematopoiesis for neutrophils, monocytes, and macrophages and damages mucosal progenitor cells, causing a temporary loss of mucosal barrier integrity. The gastrointestinal tract, which normally contains large numbers of bacteria and lesser numbers of commensal fungi, and other bacteria-carrying sources (e.g., skin, mucosa), becomes a reservoir of potential pathogens. Virtually all BMT recipients rapidly lose all T- and B-lymphocytes after conditioning, losing immune memory accumulated through a lifetime of exposure to infectious agents, environmental antigens and vaccines. Since transfer of donor immunity to BMT recipients is variable and is greatly influenced by the timing of antigen exposure in both donor and recipient, passively acquired donor immunity cannot be relied upon to provide long-term immunity against vaccine preventable diseases in BMT recipients. Without reimmunization, antibody titers to vaccine

preventable diseases such as tetanus, polio, measles, mumps, rubella, and encapsulated organisms, etc., decline over 1-4 years after allogeneic and autologous BMT (27a-e). There are no data concerning vaccine efficacy in BMT recipients. Therefore, data are insufficient to determine whether different immunization schedules should be recommended for recipients of different types of BMT. The clinical relevance of decreased antibodies to vaccine-preventable diseases in BMT recipients is not immediately apparent because few cases of vaccine-preventable diseases are reported in U.S. BMT recipients. However, vaccine preventable diseases still pose risks to the general U.S. population. In addition, there is evidence that vaccine-preventable diseases in some cases pose increased risk to BMT recipients; therefore, until further data are available, BMT recipients should be reimmunized post-BMT.

During the first month post-BMT, the major host-defense deficits include impaired phagocytosis and damaged mucocutaneous barriers. In addition, indwelling intravenous catheters are frequently placed and left *in situ* for weeks to administer parenteral medications, blood products, and nutritional supplements. These catheters serve as yet another portal of entry for opportunistic pathogens, particularly from organisms colonizing the skin such as coagulase-negative staphylococci, *Staphylococcus aureus, Candida* spp., and enterococci (28, 29).

Engraftment for both adults and children is defined as the point at which a patient can maintain a sustained absolute neutrophil count (ANC) of >500/mm^3 and sustained platelet count of 20,000 - 50,000/mm^3 lasting at least 3 consecutive days without transfusions; in unrelated allogeneic BMT recipients, engraftment occurs at a median of 22 days post-BMT (range 6-84 days) (15). BMTs are usually done in a hospital, although some providers perform autologous BMTs (e.g., using peripheral blood progenitor cells) in an outpatient setting (29a). When BMT is performed as an inpatient, the BMT recipients are usually discharged from the hospital after engraftment. In the absence of corticosteroid use, engraftment is associated with the restoration of effective phagocytic function, which results in a decreased risk of bacterial and fungal infections. However, all BMT recipients and particularly allogeneic BMT recipients, experience immune dysfunction for months after engraftment. For example, although allogeneic BMT recipients may have normal total lymphocyte counts within a few months post-BMT, they have abnormal CD4/CD8 T-cell ratios, reflecting their decreased CD4 and increased CD8 T-cell

counts (28). They may also have IgG_2, IgG_4, and IgA deficiencies for months post-BMT as well as difficulty switching from IgM to IgG production after antigen exposure (28). Immune recovery may be delayed further by CMV infection (28a).

During the first few months following BMT, recipients may develop acute GVHD which usually manifests as skin, gastrointestinal, and liver injury, and is graded on a scale of I-IV. Grade I is defined as mild and Grades II-IV are defined as moderate to severe (28, 30, 31). GVHD primarily occurs in allogeneic BMT recipients, particularly those receiving matched, unrelated donor transplants, although autologous or syngeneic BMT recipients may occasionally develop a mild, self-limited form of GVHD (22,32). GVHD is a major risk factor for infection in BMT recipients since it is associated with a delayed immunologic recovery and prolonged immunodeficiency (22). In addition, the immunosuppressive agents used for GVHD prophylaxis and treatment may make the BMT recipient even more vulnerable to opportunistic viral and fungal pathogens (33).

Some patients, particularly adult allogeneic BMT recipients, may also develop chronic GVHD. It is graded as either limited or extensive chronic GVHD (22, 34). Chronic GVHD presents similarly to autoimmune, connective-tissue disorders such as scleroderma or systemic lupus erythematosus (35) and is associated with cellular and humoral immunodeficiencies, including macrophage deficiency, impaired neutrophil chemotaxis (36), poor response to immunization (37-39), and severe mucositis (22). Risk factors for chronic GVHD include increasing age, allogeneic BMT (particularly those in which the donor is unrelated or an non-HLA identical family member)(35), and a history of acute GVHD (30, 40). Chronic GVHD was first described as occurring >100 days post-BMT, but may occur as early as 40 days post-BMT (22). Allogeneic BMT recipients with chronic GVHD have long-lasting IgA, IgG, and IgG subclass deficiencies (36, 41, 42) but normal or high total serum immunoglobulin levels (36) and poor opsonization and impaired reticuloendothelial function. Consequently, they are at even greater risk for infections (28, 34), particularly life-threatening bacterial infections from encapsulated organisms (e.g., *S. pneumoniae, H. influenzae, N. meningitidis*). After chronic GVHD resolves, which may take weeks, months, or years, cell-mediated and humoral immunity function are gradually restored.

Opportunistic Pathogens after BMT

BMT recipients develop various infections at different times post-transplant, reflecting the predominant host-defense defect(s). A timetable delineating these infections is included in Timetable 1. The timetable describes three phases of immune recovery for BMT recipients, beginning at day 0--the day of transplant. Phase 1 is the pre-engraftment phase (<30 days post-BMT); phase 2, the post-engraftment phase (30-100 days post-BMT); and phase 3, the late phase (>100 days post-BMT). Information included in the timetable can be useful in developing targeted prevention strategies.

Phase 1: Pre-engraftment phase. During the first month post-transplant, BMT recipients have two major risk factors for infection: a) prolonged neutropenia and b) breaks in the mucocutaneous barrier due to the BMT preparative regimens and frequent vascular access required for patient care. Consequently, oral, gastrointestinal, and skin flora are major sources of infection. Prevalent pathogens include *Candida* spp., and, as neutropenia continues, *Aspergillus* spp. In addition, herpes simplex virus (HSV) reactivation can also occur during this phase. During pre-engraftment, the risks for infection are the same for autologous and allogeneic BMT patients, and OIs may present as febrile neutropenia. Although a BMT recipient's first fever during pre-engraftment is likely caused by a bacterial pathogen, only rarely is an organism or site of infection identified. Instead, such infections are usually treated pre-emptively or empirically (43) until the neutropenia resolves (44). (See *Bacterial Infections* section). In persons with non-myeloid malignancies undergoing myeloablative chemotherapy and BMT, growth factors may be administered during phase I to decrease the duration of neutropenia and complications such as febrile neutropenia (45).

Phase II: Post-Engraftment. Phase II is dominated by impaired cell-mediated immunity for both allogeneic and autologous BMT recipients. The extent and impact of this defect for allogeneic BMT recipients are determined by the extent of GVHD and its immunosuppressive therapy. During engraftment, the herpes viruses, particularly cytomegalovirus (CMV), are major pathogens. At 30-100 days post BMT, CMV causes pneumonia, hepatitis, and colitis, potentiates

superinfection with a variety of opportunistic pathogens, and is intimately involved in the pathogenesis of GVHD. Other dominant pathogens during this phase include *Pneumocystis carinii* and *Aspergillus* spp.

Phase III: Late Phase. During phase III, autologous BMT recipients usually have more rapid recovery of immune function and therefore a lower risk of OIs than do allogeneic BMT recipients. Because of cell-mediated and humoral immunity defects as well as impaired reticuloendothelial system function, allogeneic BMT patients with chronic GVHD are at risk for various infections during this phase. These infections include CMV, varicella-zoster virus (VZV), Epstein-Barr virus (EBV)-related post-transplant lymphoproliferative disease (PT-LPD), community-acquired respiratory viruses (CRV), and infections with encapsulated bacteria such as *Haemophilus influenzae*, and *Streptococcus pneumoniae*.

The risk of these infections is roughly proportional to the severity of the patient's GVHD. Patients receiving mismatched allogeneic transplants have a higher incidence and severity of GVHD and therefore a higher risk of OIs in phases II and III than do patients receiving matched allogeneic BMTs. In contrast, patients undergoing autologous transplantation are primarily at risk for infection during phase I.

In summary, as with all patients, preventing infections in BMT recipients is preferable to treatment. Despite recent technological advances, however, more work is needed to optimize health outcomes for BMT recipients. Efforts to improve immune reconstitution, especially in allogeneic transplant recipients, and to prevent or resolve the immune dysregulation resulting from donor-recipient histoincompatibility remain enormous challenges for preventing recurrent, persistent, or progressive infections in BMT patients.

Table 1

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Table 2

Participant List

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Participant List

BMT meeting at CDC on March 19-20, 1997 (continued)

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30. **Patrick J. Stiff**, **M.D., Southwest Oncology Group (SWOG) Representative**, Loyola University, Maywood, IL
31. **Keith Sullivan**, **M.D.**, **American Society for Blood and Marrow Transplantation (ASBMT) Representative**, **Fred Hutchinson Cancer Research Center**, Seattle, WA
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35. **Jeffrey Wolf, M.D., Alta Bates Herrick Hospital**, Berkeley, CA
36. **Andrew Yeager, M.D., Emory University**, Atlanta, GA

Table 3

ACIP Bone Marrow Transplant Immunization Working Group Meeting,

CDC, Atlanta, GA, October 6 - 7, 1997

Name/Affiliation of non-CDC Participants

1. **Donna Ambrosino, M.D.**, BMT Guidelines Immunization Working Group, Dana-Farber Cancer Institute, Boston, MA
2. **Norman Baylor, Ph.D.**, Office of Vaccines, Research and Review, CBER/FDA, Rockville, MD
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Table 4

Evidence-Based Rating System Used in the BMT Guidelines

Categories reflecting the strength of each recommendation for or against the use of a drug or measure for the prevention of opportunistic infection in BMT patients.

Category	Definition
A	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B	Moderate evidence for efficacy--or strong evidence for efficacy, but only limited clinical benefit--supports recommendation for use. Pros and cons should be discussed, but should generally be offered.
C	Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy may not outweigh the toxicity, drug interactions, or cost of the chemoprophylaxis or alternative approaches. Optional.
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

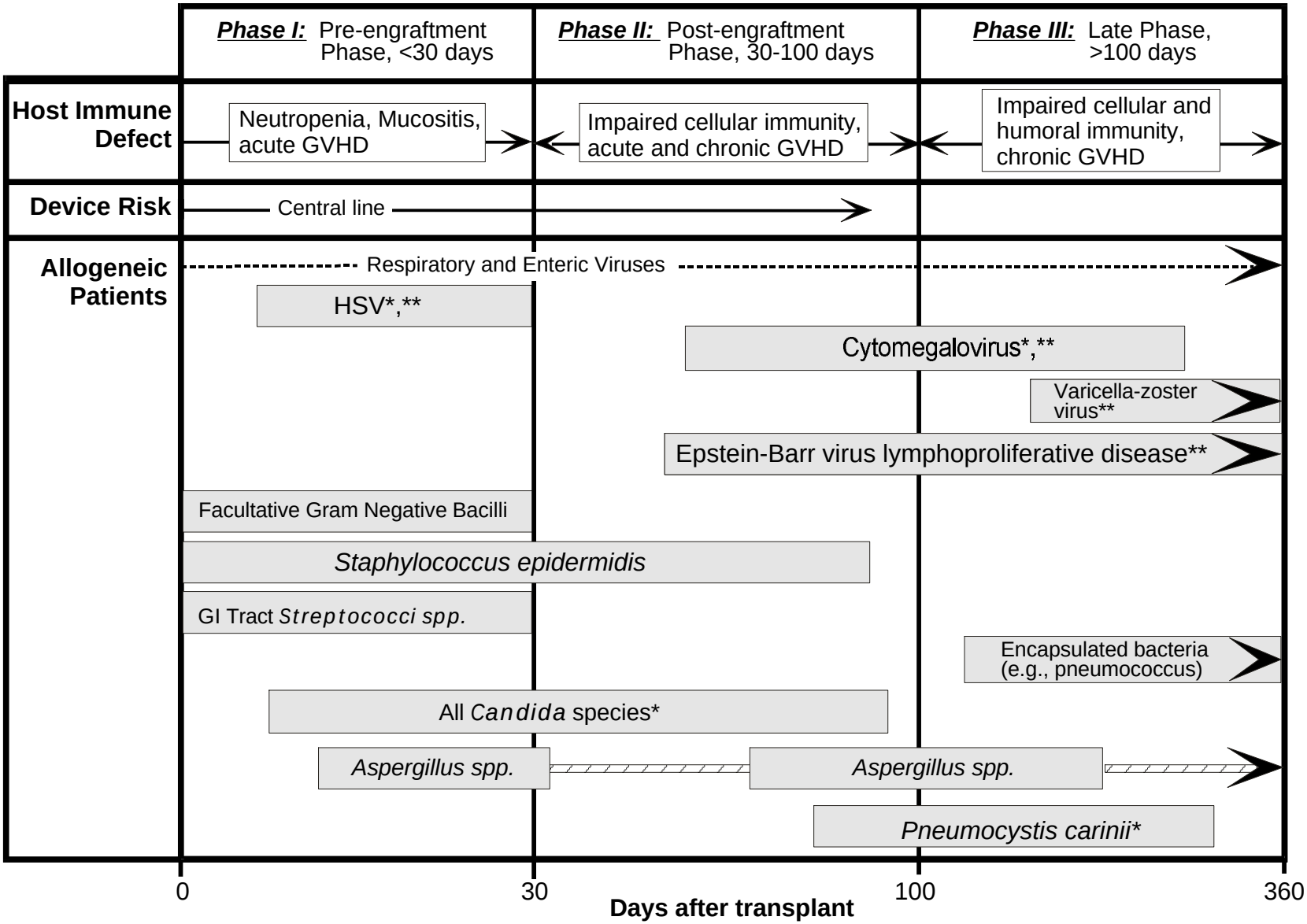
Table 5

Evidence-Based Rating System Used in the BMT Guidelines

Categories reflecting the quality of evidence forming the basis for recommendations regarding the use of a drug or measure for the prevention of opportunistic infection in BMT patients.

Category	Definition
I	Evidence from at least one properly randomized, controlled trial.
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Timetable 1: Phases of Opportunistic Infections in Allogeneic BMT Recipients



Key: * Without standard prophylaxis
** Primarily in persons who are seropositive before transplant.

Legend:
- High incidence (≥10%)
- Low incidence (<10%)
- Episodic and endemic
- Continuous risk

Introduction and Background References

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BACTERIAL INFECTIONS

I. General Bacterial Infections

A. Prevention of Exposure

1. Since bacteria are carried on the hands, health care workers (HCWs) and others in contact with BMT recipients should always follow routine appropriate hand-washing practices to avoid exposing BMT recipients to bacterial pathogens **[AIII]**. (See *Hospital Infection Control* section *II*, and *Strategies for Safe Living Following Transplantation*, section *I*).
2. Recommendations on preventing catheter infections are included in *Hospital Infection Control*, section *VIII*.
3. Recommendations on preventing exposure to specific bacterial pathogens are included in the following sections under *Hospital Infection Control* and *Strategies for Safe Living following Transplantation.*

<u>*Hospital Infection Control*</u>	
Legionella spp.	Section XI A
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Section XI B
Staphylococcus spp. with reduced susceptibility to vancomycin	Section XI C
Vancomycin-resistant enterococci (VRE) disease	Section XI D
Clostridium difficile	Section XI E
Mycobacterium tuberculosis	Section XI G

<u>*Strategies for Save Living following Transplantation*</u>	
Occupations and Hobbies	Section I
Pet Safety	Sections II, III
Food Safety - Strategies to minimize food-related illnesses	Sections III, IV
Prevention of exposure during travel	Section V

4. Routine gut decontamination is not recommended for BMT candidates (1-3) **[DIII]**.

B. Prevention of Disease

1. Prevention of Early Disease (0-100 days post-BMT)
   a. No recommendations can be made regarding the routine use of antibiotics for bacterial prophylaxis in neutropenic BMT recipients due to limited data. Although studies have shown that using prophylactic antibiotics may reduce bacteremia rates post-BMT (1), infection-related mortality rates are not reduced (2). If physicians choose to use prophylactic antibiotics in neutropenic BMT recipients, they should routinely review hospital and BMT unit antibiotic-susceptibility profiles, especially when using a single antibiotic for antibacterial prophylaxis **[BIII]**. The emergence of fluoquinolone-resistant coagulase-negative staphylococci and *E. coli* (1, 2), vancomycin intermediate *Staphylococcus aureus* (VISA) and vancomycin resistant enterococcus (VRE) are growing concerns. Vancomycin should not be used as an agent for routine bacterial prophylaxis **[DIII]**.
   b. Intravenous Gamma Globulin (IVIG)
      i. BMT physicians should **not** routinely administer IVIG products to BMT recipients for bacterial infection prophylaxis **[DII]**(although IVIG has been considered for use by some experts to produce immune modulation for GVHD prevention). However, some experts advise routine IVIG use to prevent bacterial infections in the approximately 20% - 25% of BMT recipients with unrelated marrow grafts who develop severe hypogammaglobulinemia (e.g., IgG <400mg/dl) within the first 100 days after transplant **[CIII]**. For example, BMT recipients who are hypogammaglobulinemic might receive prophylactic IVIG to prevent bacterial sinopulmonary infections (e.g., from *Streptococcus pneumoniae)***(8)[CIII]**.
      ii. For hypogammaglobulinemic allogeneic BMT recipients, BMT physicians should consider using a higher and more frequent dose than is standard for non-BMT recipients because the IVIG half-life in BMT recipients (generally 1-10 days) is much shorter than the half-life in healthy adults (generally 18-23 days) (5-7). In addition, infections may accelerate IgG catabolism. Therefore,

the IVIG dose for a hypogammaglobulinemic BMT recipient should be individualized to maintain trough serum IgG concentrations > 400-500 mg/dl (7) **[BII]**. Consequently, BMT physicians should carefully monitor trough serum IgG concentrations in these patients approximately every 2 weeks and adjust IVIG doses as needed **[BIII]**. (See *Dosing Chart*).

iii. Information on obtaining IVIG is included in the Footnote.

2. Prevention of Late Infection (> 100 days post-BMT)

a. Antibiotic prophylaxis is recommended to prevent infection with encapsulated organisms (e.g., *S. pneumoniae*, *H. influenzae*, *N. meningitidis*, etc.) in allogeneic BMT recipients with chronic GVHD for as long as active chronic GVHD treatment is given (7a) **[BIII]**. The antibiotic selection should be guided by local antibiotic resistance patterns.

b. In the absence of severe demonstrable hypogammaglobulinemia such as low IgG levels < 400 mg/dl, which may be associated with recurrent sinopulmonary infections, routine monthly IVIG administration to BMT recipients beyond 90 days post-BMT is not recommended (8)**[DI]** as a means of preventing bacterial infections.

C. Autologous BMT Recipients

Routine use of IVIG in autologous BMT recipients is not recommended (4) **[DII]**.

D. Pediatric Note

Recommendations to prevent bacterial infections are the same in pediatric and adult BMT recipients.

II. *Streptococcus pneumoniae*

A. Prevention of Exposure

Since *S. pneumoniae* circulates in the community, patients infected with *S. pneumoniae* should be cared for using standard precautions (9,10) **[BIII]** to prevent *S. pneumoniae* exposure in BMT recipients.

B. Prevention of Disease

1. Information on the currently available 23-valent pneumococcal polysaccharide

vaccine indicates limited immunogenicity in BMT recipients. However, because of its potential benefit to some, it should be administered to BMT recipients at 12 and 24 months post-BMT (11,12) **[BIII]**. (See *Immunization* section).

2. TMP-SMZ given for prophylaxis for PCP may also provide protection against pneumococcal infections. However, no data exist to support using TMP-SMZ prophylaxis in BMT recipients solely for the purpose of preventing *S. pneumoniae* disease. Many strains of S. pneumoniae are resistant to TMP-SMZ and/or penicillin. For further information on *S. pneumoniae* prophylaxis in the era of increasing penicillin-resistance, see I. B. 2a.

C. Autologous BMT Recipients

Recommendations to prevent pneumococcal infections are the same for both allogeneic and autologous BMT recipients.

D. Pediatric Notes

As with adults, pediatric BMT recipients ≥2 years of age should be given the current 23-valent pneumococcal polysaccharide vaccine because the vaccine may be effective in some **[BIII]**. However, this vaccine should not be given to children < 2 years of age because it is not effective in that age group **[DI]**.

III. *Streptococcus viridans*

A. Prevention of exposure

Since *Streptococcus viridans* colonize the oropharynx and gut, no effective method of preventing exposure is known.

B. Prevention of disease

1. Chemotherapy-induced oral mucositis is a potential source of *Streptococcus viridans* bacteremia. Consequently, before conditioning starts, dental consults should be obtained for all BMT candidates to assess their state of oral health, and to perform any needed dental procedures to decrease the risk of oral infections post-transplant (13) **[AIII]**. (See *Hospital Infection Control* section *VI).*

2. In general, BMT physicians should not use prophylactic antibiotics to prevent *Streptococcus viridans* infections **[DIII]**. Currently, no data demonstrate efficacy of prophylactic antibiotics for *Streptococcus viridans.* Furthermore, such use may select antibiotic-resistant bacteria, and, in fact, penicillin- and vancomycin-resistant strains of *Streptococcus viridans* have already been reported (14). However, when *Streptococcus viridans* infections among BMT recipients are virulent and associated with overwhelming sepsis and shock, prophylaxis may be considered **[CIII]**. Decisions regarding the use or nonuse of *Streptococcus viridans* prophylaxis should be made only after consultation with the hospital epidemiologists and/or infection control practitioners who monitor rates of nosocomial bacteremia and bacterial susceptibility **[BIII]**.
3. BMT providers should be familiar with current antibiotic susceptibilities for patient isolates from their hospitals and BMT units, including *Streptococcus viridans* **[BIII]**. Physicians should maintain a high index of suspicion for *Streptococcus viridans* disease in BMT recipients with symptomatic mucositis because early diagnosis and aggressive therapy are currently the only potential means of preventing shock when severely neutropenic BMT recipients develop *Streptococcus viridans* bacteremia (15) **[CIII]**.

IV. *Haemophilus influenzae* type b (Hib)

A. Prevention of exposure

1. Adults infected with Hib pneumonia require standard precautions (15a). Adults and children with known or suspected Hib meningitis should be placed in droplet precautions until 24 hours after they begin appropriate antibiotic therapy, after which they can be switched to standard precautions.
2. Household contacts exposed to persons with Hib disease should be given rifampin prophylaxis according to published recommendations (16, 17) **[BIII]**. (See *Dosing Chart).* This may decrease the risk of Hib transmission from household contacts to BMT recipients.

3. Pediatric household contacts of BMT recipients should be up-to-date with Hib vaccinations to prevent possible Hib exposure to the BMT recipient **[AII]**. See Immunization section, Table 2.

B. Prevention of disease

1. Although no data on vaccine efficacy in BMT recipients exist, Hib conjugate vaccine should be given to BMT recipients at 12, 14, and 24 months post-BMT **[BII]**. This vaccine is recommended because most BMT recipients have low levels of Hib capsular polysaccharide antibodies ≥4 months post-BMT (18) and allogeneic BMT recipients with chronic GVHD are at increased risk for infection from encapsulated organisms (e.g., Hib, etc.) (19, 20). (See *Immunization* section).
2. BMT recipients who are exposed to persons with Hib disease should be offered rifampin prophylaxis according to published recommendations (16) **[BIII]**. (See *Dosing Chart*).
3. BMT recipients with chronic GVHD should be given antibiotic prophylaxis. See I. B. 2a.

C. Autologous BMT recipients

Recommendations to prevent Hib infections are the same for both allogeneic and autologous BMT recipients.

D. Pediatric Notes

Recommendations for preventing Hib disease are the same for pediatric and adult BMT recipients, except that children infected with Hib pneumonia require standard precautions with droplet precautions added for 24 hours after beginning appropriate antibiotic therapy (15a, 16) **[BIII]**. Appropriate pediatric doses should be given for Hib conjugate vaccine and for rifampin prophylaxis (17). (See *Dosing Chart*).

FOOTNOTE ON IVIG

IVIG can usually be obtained from the American Red Cross Blood Services. But occasionally,

shortages occur. Physicians who have difficulty obtaining IVIG for a patient in urgent need should contact

a) the following major manufacturers of IVIG:
   Alpha Therapeutic Corporation (1-800-421-0008);
   Baxter Healthcare Corporation (1-847-940-5955);
   Bayer Corporation (1-800-288-8370);
   Centeon, L.L.C. (1-800-504-5434); and
   Novartis Pharmaceuticals Corporation (IVIG Hotline [973-503-7500] or customer service [1-800-526-0175]) or

b) The Immune Deficiency Foundation (1-800-296-4433).

Physicians who are still unable to obtain IVIG for a licensed indication may contact the Product Shortage Officer at the Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER), Office of Compliance (301-827-6220) for assistance.

Bacterial Infections References

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VIRAL INFECTIONS

I. CYTOMEGALOVIRUS (CMV)

A. Prevention of Exposure

1. BMT candidates should be tested for the presence of serum anti-CMV IgG antibodies before transplantation to determine their risk of primary CMV infection and reactivation post-BMT **[AIII]**.
2. BMT recipients and candidates should avoid sharing cups, glasses, and eating utensils with others including family members to decrease the risk of CMV exposure **[BIII]**.
3. Sexually active patients who are not in long-term monogamous relationships should always use latex condoms during sexual contact to reduce their risk of exposure to CMV and other sexually transmitted pathogens **[AII]**. However, even long-time monogamous pairs can be discordant for CMV infections. Therefore, during periods of immunocompromise, sexually active BMT recipients in such relationships may consider using latex condoms during sexual contact to reduce the risk of exposure to this sexually transmitted OI **[CIII]**.
4. After handling or changing diapers, or after wiping oral and nasal secretions, BMT candidates and recipients should practice regular hand washing to reduce the risk of CMV exposure **[AII]**.
5. CMV seronegative recipients of allogeneic stem cell transplants should receive only leukocyte-reduced or CMV-seronegative red cells and/or leukocyte-reduced platelets ($< 1 \times 10^{6}$ leukocytes/unit) to prevent transfusion-associated CMV infection (1) **[AI]**.
6. All HCWs should wear appropriate gloves when handling blood products or other potentially contaminated biologic materials **[AII]**.
7. BMT patients who are known to be excreting CMV should be placed under standard precautions (1a) for the duration of CMV excretion to avoid possible transmission to CMV-seronegative BMT recipients and candidates **[AIII]**. Clinicians are cautioned that CMV excretion may be episodic and/or prolonged.

B. Prevention of Disease and Disease Recurrence

BMT recipients at risk for CMV disease post-BMT (i.e., all CMV-seropositive BMT

recipients, and all CMV-seronegative recipients with a CMV-seropositive donor) should be placed on a CMV disease prevention program from engraftment to day +100 post-BMT (Phase II) **[AI]**. Clinicians should use either prophylaxis or pre-emptive treatment with ganciclovir for allogeneic BMT recipients **[AI]**. In selecting a CMV disease prevention strategy, physicians should consider the risks and benefits of each strategy, the needs and the condition of the individual patient, and the hospital's virology laboratory support capability.

1. Prophylaxis strategy against early CMV (< 100 days post-BMT) for allogeneic BMT recipients

   The prophylaxis strategy involves administering ganciclovir prophylaxis to all at risk allogeneic BMT recipients throughout Phase II (i.e., from engraftment to day +100 post-BMT). The induction course is usually started at engraftment **[AI]**, although some centers may add a brief prophylactic course during pre-BMT conditioning **[CIII]**. (See *Dosing Chart*).

2. Pre-emptive strategy against early CMV (< 100 days post-BMT) for allogeneic BMT recipients

   a. The pre-emptive strategy restricts ganciclovir use to those patients who have evidence of CMV infection post-BMT. It requires the use of sensitive and specific laboratory tests to rapidly diagnose CMV infection post-BMT and to enable immediate administration of ganciclovir once CMV infection has been detected. At risk allogeneic BMT recipients should be screened at least weekly from day +10 to day +100 post-BMT (Phase II) for the presence of CMV viremia or antigenemia **[AIII]**. BMT physicians should select one or more of the following diagnostic tests to determine the need for pre-emptive treatment:

      i. Detection of CMV pp65 antigen in leukocytes (antigenemia) (2,3). Currently, this test is preferred for screening for pre-emptive treatment because it is more rapid and sensitive than culture, and has good positive predictive value (2,3,4).

      ii. Direct detection of CMV-DNA by polymerase chain reaction (PCR) (5). The

CMV-DNA PCR is very sensitive but has a low positive predictive value (2). Although it is less sensitive than whole blood or leukocyte PCR, plasma CMV-DNA PCR is particularly useful during neutropenia, when the number of leukocytes/slide is too low to allow CMV pp65 antigenemia testing.

Virus culture of urine, saliva, blood, or bronchoalveolar washings by rapid shell-vial culture (6) or routine culture (7, 8) can be used, however viral culture techniques are less sensitive than CMV-DNA PCR or CMV pp65 antigenemia tests. Also, rapid shell-viral cultures require at least 48 hours and routine viral cultures may require several weeks to obtain final results. Thus, viral culture techniques are less satisfactory than PCR or antigenemia tests. A center without access to PCR or antigenemia tests should use prophylaxis rather than preemptive therapy for CMV disease prevention (8a)**[BII]**.

b. Allogeneic BMT recipients who are ≤100 days post-BMT (during Phase II) should begin pre-emptive treatment with ganciclovir if CMV viremia or antigenemia is detected **[BIII]**. Once pre-emptive treatment has been started, maintenance ganciclovir is usually continued until at least 100 days post-BMT **[BII]**. Some studies suggest a shorter course of ganciclovir (e.g., for 3 weeks or until negative PCR or antigenemia occurs)(8b-d), may provide adequate CMV prevention with less toxicity, but routine weekly screening by pp65 antigen or PCR test is necessary after stopping ganciclovir because CMV reactivation can still occur **[BIII]**.

c. At this time, only the intravenous formulation of ganciclovir has been approved for use in the CMV prophylactic or pre-emptive strategies **[BIII]**. No recommendation for oral ganciclovir use in BMT recipients can be made because clinical trials evaluating its efficacy are still in progress. One group has used ganciclovir and foscarnet on alternate days for CMV prevention (8e), but no recommendation can be made regarding this strategy due to limited data.

d. Patients who are intolerant to ganciclovir should be given foscarnet instead (8f) **[BII]**. (See *Dosing Chart*).

e. BMT recipients receiving ganciclovir should have absolute neutrophil counts

(ANCs) checked at least twice weekly **[BIII]**. Some experts recommend managing ganciclovir-associated neutropenia by adding granulocyte-colony stimulating factor (G-CSF) (9) or temporarily stopping ganciclovir for ≥2 days if the patient's ANC is <1000 **[CIII]**. Ganciclovir may be restarted when the patient's ANC is ≥1000 for 2 consecutive days. Alternatively, some experts recommend substituting foscarnet for ganciclovir if a) the BMT recipient is still CMV viremic or antigenemic or b) the ANC remains <1000 for >5 days after ganciclovir has been stopped **[CIII]**. (See *Dosing Chart*). Because neutropenia accompanying ganciclovir administration is usually brief, such patients do not require antifungal or antibacterial prophylaxis **[DIII]**.

e. Some experts suggest that BMT recipients requiring simultaneous prophylaxis for both CMV and HSV post-BMT may be given ganciclovir alone because ganciclovir has *in vitro* activity against CMV and HSV 1 and 2 (9a) **[CIII],** although ganciclovir has not been approved for use against HSV.

f. The preemptive strategy is preferred over prophylaxis for CMV seronegative BMT recipients of seropositive donor cells (D+/R-) due to the low incidence of active CMV infection if screened or filtered blood product support is used **[BII]**.

3. Prevention of late CMV disease (≥100 days post-BMT) in allogeneic BMT recipients
Currently, no benefit has been documented from routinely giving all BMT recipients ganciclovir prophylaxis >100 days post-BMT (during Phase III). However, persons with high risk for late CMV disease should be routinely screened every other week for evidence of CMV reactivation from 100 days post-BMT as long as significant immunocompromise persists **[BIII]**. Risk factors for late CMV disease include allogeneic BMT accompanied by chronic GVHD, steroid use, low CD_4 counts, delay in high avidity anti-CMV antibody, and high risk recipients of matched unrelated or T-cell depleted BMTs, etc. (9b-f). If CMV is still detectable by routine screening at ≥100 days post-BMT, ganciclovir should be continued until CMV is no longer detectable **[AI]**. If low-grade CMV antigenemia (<5 positive cells/slide) is detected on routine screening, the antigenemia test should be repeated in 3 days **[BIII]**. If CMV antigenemia

indicates ≥5 cells/slide or the shell-vial culture detects CMV viremia, a 3-week course of pre-emptive ganciclovir treatment should be given **[BIII]**. (See *Dosing Chart*). Current investigational strategies for preventing late CMV disease include the use of targeted prophylaxis with antiviral drugs and cellular immunotherapy for those with deficient or absent CMV-specific immune function.

4. Ganciclovir-resistant CMV

   If viremia persists after 4 weeks of ganciclovir pre-emptive therapy or if the level of antigenemia continues to rise after 3 weeks of such therapy, ganciclovir-resistant CMV should be suspected. If CMV viremia recurs during continuous treatment with ganciclovir, some experts recommend restarting ganciclovir induction (10) or stopping ganciclovir and starting foscarnet **[CIII]**. There are only limited data regarding the use of foscarnet in BMT recipients either for CMV prophylaxis or pre-emptive therapy (8e, 8f).

5. Other methods of preventing CMV disease

   a. Infusion of donor-derived CMV-specific clones of CD8+ T cells into the transplant recipient is currently being evaluated under FDA Investigational New Drug (IND) authorization; therefore, no recommendation can be made at this time.

   b. Although high-dose acyclovir has been demonstrated in a large cooperative study to have some efficacy for preventing CMV disease (11) its utility is limited in a setting where more potent anti-CMV agents such as ganciclovir are used (11a). Acyclovir is not effective in preventing CMV disease after autologous BMT (12) and is therefore not recommended for CMV pre-emptive therapy **[DII]**. Consequently, acyclovir's pro-drug valaciclovir, while under study for use in BMT recipients, is presumed to be less effective than ganciclovir against CMV and is therefore is currently not recommended for CMV disease prevention **[DII]**.

   c. Although many BMT units continue to use IVIG for immune modulation, IVIG is not recommended for CMV disease prophylaxis in BMT recipients **[DI]**.

   d. Cidofovir, a nucleoside analog, is approved by FDA for the treatment of AIDS-associated CMV retinitis. The drug's major disadvantage is toxicity, which includes renal dysfunction and myelosuppression. Cidofovir is currently in Phase 1 trial for use

in BMT recipients, and recommendations for its use cannot be made at this time.

C. Autologous BMT Recipients

1. The use of CMV-negative or leukocyte-reduced blood products is not routinely required for all autologous BMT recipients because most have a substantially lower risk of CMV disease. However, use of CMV negative or leukocyte reduced blood products may be considered in CMV seronegative autologous BMT recipients **[CIII]**.
2. CMV-seropositive autologous BMT recipients should be considered for pre-emptive therapy if they have underlying hematologic malignancies such as lymphoma or leukemia, are receiving intense conditioning regimens or graft manipulation, or have recently received fludarabine or 2-chlorodeoxyadenosine (2-CDA) **[BIII]**. This subgroup of at-risk autologous BMT recipients should be monitored weekly from engraftment until day 60 post-BMT for CMV reactivation, preferably with quantitative CMV pp65 antigen (3), or quantitative PCR **[BII]**.
3. High risk autologous BMT recipients who develop CMV antigenemia (i.e., blood levels of $\geq$5 positive cells/slide) should receive 3 weeks of pre-emptive treatment with ganciclovir or foscarnet (3) **[BII]**. (See *Dosing Chart*).
4. The prophylactic approach to CMV disease prevention is not appropriate for CMV-seropositive autologous BMT recipients.

D. Pediatric Note

Indications for the use of CMV prophylaxis or pre-emptive treatment are the same in children as in adults.

II. EPSTEIN-BARR VIRUS (EBV)

A. Prevention of Exposure

All transplant candidates, but particularly those who are EBV-seronegative, should be advised of behaviors that may decrease the likelihood of EBV exposure **[AII]**. For example, BMT recipients and candidates should follow good hygienic practices, such as frequent hand washing **[AIII]** and avoiding sharing cups, glasses, and eating utensils with others (18) **[BIII]**, and should avoid contact with potentially infected

respiratory secretions and saliva (18) **[AII]**.

B. Prevention of Disease

Infusion of donor-derived, EBV-specific cytotoxic T-lymphocytes (CTLs) has shown promise in the prophylaxis of EBV-lymphoma in recipients of T-cell-depleted unrelated/ mismatched allogeneic BMT (13, 19). However, insufficient data are available to make a recommendation regarding its use. Prophylaxis or pre-emptive therapy with acyclovir is not recommended due to lack of efficacy (16, 17) **[DII]**.

III. HERPES SIMPLEX VIRUS (HSV)

A. Prevention of Exposure

1. BMT candidates should be tested for serum anti-HSV IgG before transplant **[AIII]**, however, type specific anti-HSV IgG serology testing is not necessary.
2. All BMT candidates, and especially those who are HSV seronegative, should be informed of the importance of avoiding HSV infection while immune compromised and should be advised of behaviors which will decrease the likelihood of HSV exposure **[AII]**. BMT recipients and candidates should avoid sharing cups, glasses, and eating utensils with others **[BIII]**. Sexually active patients who are not in a long-term monogamous relationship should always use latex condoms during sexual contact to reduce the risk of exposure to HSV as well as other sexually transmitted pathogens **[AII]**. However, even long-time monogamous pairs can be discordant for HSV infections. Therefore, during periods of immunocompromise, sexually active BMT recipients in such relationships may consider using latex condoms during sexual contact to reduce the risk of exposure to this sexually transmitted OI **[CIII]**.
3. Persons with disseminated, primary, or severe mucocutaneous HSV disease should be placed under contact precautions for the duration of the illness (1a) **[AI]**.

B. Prevention of Disease

1. Acyclovir
   a. Acyclovir prophylaxis should be offered to all HSV-seropositive allogeneic BMT recipients to prevent HSV reactivation during the early post-transplant period

(20-24) **[AI]**. A standard approach is to begin acyclovir prophylaxis at the start of the conditioning therapy and continue until engraftment occurs or until mucositis resolves (whichever is longer, or approximately 30 days post-BMT) **[BIII]**. (See *Dosing Chart*). In the absence of supportive data from controlled studies, routine use of antiviral prophylaxis to prevent HSV for longer than 30 days post-BMT is not recommended **[DIII]**.

b. Routine acyclovir prophylaxis is not indicated in HSV-seronegative BMT recipients, even if the donors are HSV seropositive **[DIII]**.

c. Some experts suggest that BMT recipients requiring simultaneous prophylaxis for both CMV and HSV post-BMT may be given ganciclovir prophylaxis alone (8a)**[CIII]** although ganciclovir has not been approved for use against HSV.

2. Other drugs

a. Some experts recommend valaciclovir for HSV prevention in BMT recipients **[CIII]** but controlled trial data in BMT recipients are lacking (25). (See *Dosing Chart*). Physicians wishing to consider valaciclovir use in BMT recipients with renal impairment should exercise caution and decrease doses as needed **[BIII]**.

b. Because of its significant renal and infusion-related toxicity, foscarnet is not recommended for routine HSV prophylaxis in BMT recipients **[DIII]**.

c. Data on safety and efficacy of famciclovir in BMT recipients are not available. Therefore, no recommendations for HSV prophylaxis with famciclovir can be made at this time.

C. Prevention of disease recurrence

HSV prophylaxis lasting > 30 days post-BMT may be considered for persons with frequent recurrent HSV **[CIII]**. (See *Dosing Chart*).

D. Autologous BMT Recipients

Acyclovir may be considered during phase I for administration to HSV-seropositive autologous BMT recipients who are likely to develop significant mucositis from the conditioning regimen **[CIII]**.

E. Pediatric Notes

1. Indications for HSV prophylaxis are the same for children as in adults.
2. Antiviral prophylaxis doses should be modified for use in children. (See *Dosing Chart*).
3. There are no published data on valaciclovir safety and efficacy in children.

IV. VARICELLA ZOSTER VIRUS (VZV)

A. Prevention of Exposure

1. BMT candidates should be tested for the presence of serum anti-VZV IgG antibodies **[AIII]**. However, VZV seropositivity does not protect BMT recipients from developing VZV disease (27, 27a), and latent VZV may be present in persons even without detectable serum anti-VZV IgG antibodies (27).
2. All BMT candidates and recipients, particularly those who are VZV-seronegative, should be informed of the potential seriousness of VZV disease in immuno-compromised persons and advised of strategies to decrease their risk of VZV exposure (26-30) **[AII]**.
   a. Although most VZV disease post-BMT is thought to be due to reactivation of endogenous VZV, BMT candidates and recipients who are VZV-seronegative, or VZV-seropositive and immunocompromised, should avoid exposure to persons with active VZV infections (31) **[AII]**.
   b. Household contacts and visitors who do not have a documented history of varicella infection or who are VZV seronegative should receive VZV vaccination **[AIII]**. Ideally, VZV-susceptible household contacts and potential visitors of immuno-compromised BMT recipients should be immunized as soon as the decision to perform a BMT is made or at least 4 weeks before the conditioning regimen begins or at least 6 weeks (42 days) before the BMT is performed **[BIII]**. (See *Immunization* section).
   c. BMT recipients and candidates undergoing conditioning therapy should avoid contact with any VZV vaccine recipient who develops a rash following VZV immunization **[BIII]**. When it occurs, this rash usually presents 7-14 days after

VZV immunization (range 5-35 days) (33). However, to date, no serious disease has been reported in immunocompromised patients from transmission of VZV vaccine virus.

d. All BMT recipients with VZV disease should be placed under airborne and contact precautions (1a) **[AII]**. Contact precautions should be continued until all skin lesions are crusted. Airborne precautions should be instituted 10 days after exposure to VZV and continued until 21 days after last exposure (or 28 days post-exposure if the patient received VZIG) (1a) **[AI]**.

B. Prevention of Disease

1. Varicella Zoster Immune Globulin (VZIG)

   a. VZV-seronegative BMT recipients should be given VZIG as soon as possible and ideally **within 96 hours after close contact with a person with either chickenpox or shingles** if the BMT recipient is not immunocompetent (i.e., patient is < 24 months post-BMT, is ≥24 months post-BMT and on immunosuppressive therapy, or has chronic GVHD) **[AII]**.

   b. Because of the high morbidity of VZV-associated disease in severely immuno-compromised BMT recipients and until further data are available, BMT physicians should administer VZIG to all VZV-seronegative BMT recipients or candidates undergoing conditioning therapy who are exposed to a VZV vaccinee with a varicella-like rash **[BIII].** This is recommended because the vaccinee may be unknowingly incubating wild-type varicella, especially during the first 14 days after varicella vaccination.

   c. If VZV-seronegative BMT recipients or candidates undergoing conditioning therapy are exposed to varicella ≥3 weeks after receiving VZIG, they should be given another dose of VZIG (29) **[BIII]**.

   d. For patients who are VZV-seropositive, administration of VZIG is not recommended after exposure to wild-type VZV **[DIII]**.

2. Antiviral Drugs

   a. Any BMT recipient or candidate undergoing conditioning therapy who develops a

VZV-like rash following exposure to a person with wild-type varicella or shingles should receive pre-emptive antiviral drug therapy, (e.g., acyclovir) until at least 2 days after all lesions have crusted **[BIII]**. (See *Dosing Chart*).

b. Any BMT recipient or candidate undergoing conditioning therapy who develops a VZV-like rash following exposure to a VZV vaccinee with a rash should be given IV acyclovir pre-emptively to prevent severe, disseminated VZV disease **[BII]**. Acyclovir should be given until 2 days after all lesions have crusted.

c. Long-term acyclovir prophylaxis to prevent recurrent VZV infection (e.g., during the first 6 months post-BMT) is not routinely recommended (34-36) **[DIII]**, however, it could be considered in BMT recipients patients with severe, long-term immunodeficiency **[CIII]**.

d. When acyclovir resistance occurs among patients, BMT physicians should use foscarnet for pre-emptive treatment of VZV disease (37) **[BIII]**.

e. Some experts recommend valaciclovir for VZV prevention in BMT recipients because it requires lower and less frequent doses than acyclovir **[CIII]**. (See *Dosing Chart* and *HSV* section). Physicians wishing to consider valaciclovir use in BMT recipients with renal impairment should exercise caution and decrease doses as needed **[BIII]**.

f. There are no data demonstrating safety and efficacy of pre-emptive treatment of famciclovir against *Herpes zoster* in BMT recipients. Consequently, no recommendation for its use in BMT recipients can be made at this time.

3. Live-attenuated VZV vaccine

a. Varicella seronegative BMT candidates without cell mediated immune defects may be offered varicella immunization (29, 29a, 30, 33a) **[BIII**. If the live, attenuated VZV vaccine is administered to BMT candidates without cell mediated immune defects, it should be given as soon as the decision is made to perform a BMT and at least 4 weeks before the conditioning regimen begins (37a) and at least 6 weeks (42 days) before the BMT is performed **[BIII]**. (See *Immunization* section). VZV vaccine use is contra-indicated in BMT recipients who are < 24 months post-BMT (33a) **[EIII]**. Use of VZV

vaccine in BMT recipients is restricted to research protocols for recipients who are ≥24 months post-BMT who are presumed immunocompetent. Further research is needed to determine the safety, immunogenicity, and efficacy of VZV vaccine in BMT recipients.

b. An inactivated VZV vaccine has been used investigationally in BMT recipients (38). However, more studies are needed before a recommendation regarding its use can be made.

C. Autologous BMT Recipients

The recommendations for VZV prevention are the same for allogeneic and autologous BMT recipients.

D. Pediatric Note

Recommendations for preventing VZV disease in pediatric and adult BMT recipients are the same, except that appropriate dose adjustments for VZIG should be made for pediatric BMT recipients **[AIII]**. (See *Dosing Chart*).

V. COMMUNITY RESPIRATORY VIRUSES (CRV): INFLUENZA, RESPIRATORY SYNCYTIAL VIRUS (RSV), PARAINFLUENZA VIRUS AND ADENOVIRUS

A. Prevention of Exposure

1. General

Preventing CRV exposure is critical to preventing CRV disease (39, 40). Some experts recommend that BMT providers routinely conduct CRV surveillance among BMT recipients to detect outbreaks and implement infection control measures as early as possible **[CIII]**. To prevent nosocomial CRV transmission, BMT recipients and their health care workers (HCW) should always follow BMT infection control guidelines **[AIII]**. (See *Hospital Infection Control* section *XI.* and *Strategies for Safe Living* section *I.*) At a minimum, all hospitalized BMT recipients and candidates undergoing conditioning therapy should be screened daily for signs and symptoms of CRV (e.g., upper respiratory infection [URI] and/or lower respiratory infection [LRI]). BMT recipients with URI and/or LRI symptoms should be placed under contact precautions to avoid transmitting infection to other BMT candidates and

recipients as well as to HCW and visitors until the etiology of illness is identified (1a) **[BIII]**. Optimal isolation precautions can be modified as needed once the etiology is identified (1a). BMT recipients and candidates, their family members and visitors, and all HCW should be informed about CRV infection control measures and the potential severity of CRV infections in BMT recipients (39-48) **[BIII]**. HCWs and visitors with URI symptoms should be restricted from contact with BMT recipients and BMT candidates undergoing conditioning therapy to minimize the risk of CRV transmission **[AIII]**. See *Hospital Infection Control* section *XI.*

2. Influenza
    a. To prevent influenza exposure among BMT recipients and candidates, influenza vaccination of household contacts is strongly recommended during each influenza season beginning in the season before the transplant and continuing up to at least 24 months post-BMT (49) **[AI]**. All household contacts of BMT recipients who remain immunocompromised $\geq$24 months post-BMT should continue to be vaccinated annually as long as the BMT recipient's immunocompromise persists (49) **[AI]**. Seasonal influenza vaccination is strongly recommended for healthy close contacts and HCW of BMT recipients (50, 51) **[AI]**. (See *Immunization* section, *Table 2*).
    b. During influenza A outbreaks, healthy close contacts of BMT recipients, including HCWs, should receive amantadine or rimantadine chemoprophylaxis for 2 weeks following influenza vaccination **[BIII]**. Such therapy will prevent transmission of wild-type influenza A to BMT recipients while the vaccinee develops an immunologic response to the vaccine. However, if a nosocomial outbreak occurs with an influenza A strain which is not contained in the available influenza vaccine, all healthy close contacts of and HCWs caring for BMT recipients and candidates should be given influenza A chemoprophylaxis with amantadine or rimantadine until the end of the outbreak (49) **[BIII]**.
    c. Patients with influenza should be placed under droplet and standard precautions (1a) **[AIII]**.

B. Prevention of Disease

BMT physicians should determine the etiology of a URI in a BMT recipient or candidate undergoing conditioning therapy, if possible, since RSV, influenza, parainfluenza, adenovirus URIs, etc. may progress to more serious LRI, and some of these may be amenable to treatment **[BIII]**. Appropriate diagnostic samples include nasopharyngeal (NP) washes, swabs, or aspirates, throat swabs, and bronchoalveolar lavage (BAL) fluid. BMT candidates presenting with URI symptoms at the time conditioning therapy is scheduled to start should have their conditioning regimen postponed until the URI resolves, if possible, because the URI may progress to LRI during immunosuppression (40, 42, 46, 46a) **[BIII]**. BMT conditioning need not be postponed in BMT candidates with a rhinovirus URI because this has not been reported to progress to LRI in BMT recipients **[DIII]**.

1. Influenza
    a. Life-long seasonal influenza vaccination is recommended for all BMT candidates and recipients, beginning during the influenza season pre-BMT and resuming no earlier than 6 months post-BMT **[BIII]**. However, influenza vaccinations given to BMT recipients less than 6 months post-BMT are unlikely to be beneficial and are not recommended **[DII]**.
    b. BMT recipients who are less than 6 months post-BMT should receive chemo-prophylaxis with amantadine or rimantadine during community or nosocomial influenza A outbreaks **[BIII],** but these drugs are not effective against influenza B. BMT recipients who are between 6 months and 24 months post-BMT or >24 months post-BMT and still significantly immunocompromised (i.e., are receiving immunosuppressive therapy, have had a relapse of their underlying disease or have GVHD) during such outbreaks and have not yet received an influenza vaccination during the current influenza season should be vaccinated against influenza immediately **[BIII]**. In addition, chemoprophylaxis with amantadine or rimantadine may be considered for 2 weeks after influenza vaccination in these BMT recipients during a nosocomial or community influenza A outbreak to allow sufficient time for the patient to develop an immunologic

response to the vaccination **[CIII]**. Influenza A chemoprophylaxis with amantadine or rimantadine has been suggested for all influenza A-exposed BMT recipients who are <24 months post-BMT or ≥24 months post-BMT and significantly immunocompromised regardless of vaccination history, because of their likely suboptimal immunologic response to influenza vaccine (50,51). However, no recommendation regarding such chemoprophylaxis can be made at this time because of the lack of data. For BMT recipients who are ≥24 months post-BMT and immunocompetent (i.e., not on immunosuppressive drugs and without relapse or GVHD), only seasonal influenza vaccination is recommended **[BIII]**.

c. To prevent severe disease, early pre-emptive therapy with amantadine or rimantadine has been suggested for BMT recipients with unexplained acute URI or LRI symptoms during a community or nosocomial outbreak of influenza A (49). However, the safety and effectiveness of this strategy have not been evaluated, and data are insufficient to make a recommendation.

d. Intravenous and aerosol ribavirin, neuraminadase inhibitors (51-54), and antiviral drug-combination therapy (e.g., rimantadine or amantadine with Ribavirin or interferon) (55) have been proposed for early treatment of influenza A in BMT recipients to prevent severe disease. However, these drugs remain investigational for this indication, and therefore no recommendation for use of these agents in BMT recipients can be made at this time.

2. RSV

a. The respiratory secretions of any hospitalized BMT candidate or recipient who develops signs and/or symptoms of CRV infection should be tested promptly by viral culture and rapid diagnostic tests for RSV **[BIII]**. If negative, testing should be repeated every 3 days as long as the patient remains symptomatic **[BIII]**. This is important because of the high morbidity and mortality of RSV disease in BMT recipients (56, 57). BMT recipients, especially those who are pre-engraftment and at highest risk for severe RSV pneumonia, should be diagnosed early (i.e., during RSV

URI) and supported aggressively to prevent fatal RSV disease **[BIII]**.

b. Although a definitive, uniformly effective pre-emptive therapy for RSV infection in BMT recipients has not been identified, several strategies have been proposed. These include use of *aerosolized* ribavirin (57, 58), RSV antibodies (i.e., passive immunization with high RSV titered IVIG or RSV immunoglobulin) in combination with aerosolized ribavirin (46, 59), and RSV monoclonal antibody (60). Clinical trials are currently underway to evaluate the efficacy of these strategies. No recommendation regarding the optimal method for RSV prevention and pre-emptive therapy can be made at this time due to limited data.

c. Current data do not support use of intravenous ribavirin for pre-emptive therapy for RSV pneumonia in BMT recipients (61)**[DIII]**.

d. No commercially licensed vaccines against RSV are currently available.

3. Parainfluenza virus, adenovirus

a. Immunoprophylaxis, chemoprophylaxis, and pre-emptive treatment for parainfluenza virus and adenovirus infections in BMT recipients have been suggested (62, 63). However, no recommendation can be made at this time because of insufficient data.

b. No commercially licensed vaccines against parainfluenza or adenovirus are currently available.

C. Pediatric Note

In general, the recommendations for preventing CRV infection or disease and its recurrence in BMT recipients and candidates apply to both children and adults (64-67), but with appropriate adjustments in antiviral drug and influenza vaccine doses for children. (See *Dosing Chart*).

1. Influenza

a. Annual seasonal influenza immunization is recommended for pediatric BMT recipients and candidates $\geq$ 6 months of age **[BIII]**.

b. Children <9 years of age who are receiving influenza vaccination for the first time require two doses administered at least 1 month apart **[AI]**.

c. Healthy children who receive influenza vaccination for the first time may not

develop protective antibodies until 2 weeks after receipt of the second dose of influenza vaccine. Therefore, during an influenza A outbreak, pediatric BMT recipients < 9 years of age who are ≥6 months post-BMT and receiving their first influenza vaccination should be given at least 6 weeks of influenza A chemoprophylaxis following the first dose of influenza vaccine (49) **[BIII]**. (See *Dosing Chart* and *Immunization* section).

d. Amantadine and rimantadine should not be given to children < 1 year of age (49, 64) **[DIII]**.

2. RSV

a. To prevent RSV disease, some experts recommend substituting RSV-IVIG for IVIG during RSV season for pediatric BMT recipients (i.e., < 18 years of age) who receive routine IVIG therapy (67), (i.e., those with hypogammaglobulinemia) **[CIII]**. (See *Bacterial Infections* section, *Immunization* section Table 4, and *Dosing Chart*).

b. Some experts recommend that pediatric BMT recipients (i.e., < 18 years of age) with RSV be considered for pre-emptive therapy (e.g., during URI, early LRI) with aerosolized ribavirin **[CIII]**, although this remains controversial (67). (See *Dosing Chart*).

3. Adenovirus

Droplet and contact precautions for the duration of illness are required for pediatric patients for the duration of illness (1a) **[AIII]**.

D. Autologous BMT Recipients

The recommendations for preventing influenza are the same for both allogeneic and autologous BMT recipients.

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Footnote on VZIG

VZIG is distributed by the American Red Cross except in Massachusetts, where it is distributed by the Massachusetts Public Health Biologic Laboratories (now a unit of the University of Massachusetts) (19). Specific information on where to obtain VZIG is contained in:

CDC. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45(No. RR-11):1-36, or <http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00043082.htm>.

FUNGAL INFECTIONS

I. General Fungal Disease

A. Prevention of Exposure

BMT recipients and candidates undergoing conditioning therapy should avoid contact with areas and substances, including foods, which may increase their risk of fungal exposures **[BIII]**. These include excavation sites, areas of household or building construction or renovation, chicken coops, caves, potentially contaminated soil, and foods which may contain molds such as cheese. (See *Hospital Infection Control,* and *Strategies for Safe Living* sections *II.* and *VI.*)

B. Prevention of disease

1. Growth factors such as GM-CSF and G-CSF shorten the duration of neutropenia post-BMT (1). However, there are no data indicating that growth factors effectively reduce the incidence of invasive fungal disease. Therefore, no recommendation for use of growth factors solely for prophylaxis against invasive fungal disease can be made at this time.
2. Topical antifungal drugs which are applied to the skin or mucosa but do not affect blood levels (e.g., nystatin or clotrimazole) may reduce fungal colonization in the area of application. However, these agents have not been shown to prevent the development of locally invasive or disseminated yeast infections (e.g., candidiasis) or mold infections (e.g., aspergillosis), and are not recommended for their prophylaxis **[DII]**.
3. Performing fungal surveillance cultures is not indicated for asymptomatic BMT recipients (2, 2a, 2b) **[DII]** but cultures should be obtained from symptomatic BMT recipients **[BIII]**. (See *Hospital Infection Control,* section *X.)*

II. Yeasts

A. Prevention of exposure

Invasive candidiasis is usually caused by dissemination of endogenous *Candida* spp. that have colonized a patient's gastrointestinal tract (3). Consequently, most methods of preventing exogenous yeast exposure usually do not prevent post-BMT invasive yeast

infections. However, since *Candida spp.* can be carried on the hands, HCWs and others in contact with BMT recipients should follow routine appropriate hand-washing practices to safeguard patients from such exposure **[AIII]**. (See *Hospital Infection Control* section *II,* and *Strategies for Safe Living Following Transplantation*, section *I*).

B. Prevention of disease

1. Allogeneic BMT recipients should be given fluconazole prophylaxis to prevent invasive disease with fluconazole-susceptible *Candida* spp. during neutropenia, especially in centers where *C. albicans* is the predominant cause of invasive fungal disease pre-engraftment **[AI]**. (See *Dosing Chart*). Since most candidiasis occurs during Phase I (4), Fluconazole 400 mg qd (po or iv) qd should be administered (4,5) from the day of BMT until engraftment **[AII]**. However, fluconazole is not effective against several fluconazole-resistant *Candida* spp., including *C. krusei* (6) and fluconazole-resistant *C. glabrata*, and is therefore not recommended for their prevention **[DI]**. Further studies are needed to determine the optimal duration of fluconazole prophylaxis.
2. Preliminary studies have shown that low dose fluconazole prophylaxis (100-200 mg/day po) in neutropenic patients is has variable efficacy in preventing candidiasis (7). Therefore it is not recommended for BMT recipients **[DII]**.
3. Oral, nonabsorbable antifungal drugs, including oral amphotericin B (500 mg suspension every 6 hours), nystatin, and clotrimazole troches, may reduce superficial colonization and control local mucosal candidiasis, but have not been demonstrated to reduce invasive candidiasis. Therefore, use of such products is optional **[CIII]**

C. BMT recipients with yeast disease diagnosed pre-BMT

In general, BMT candidates with candidemia or invasive candidiasis can safely receive transplants (8) if a) their infection was diagnosed early and treated immediately and aggressively with amphotericin B (or alternatively with appropriate doses of fluconazole, if the organism is susceptible), and b) evidence of disease control is documented by serial CT scans before the transplant **[BIII]**. Such patients should continue receiving therapeutic doses of an appropriate antifungal drug after engraftment (throughout Phase I) **[BII]** and until a careful review of clinical, laboratory, and serial CT scans verifies resolution of

candidiasis **[BII]**.

D. Autologous BMT Recipients

Since autologous BMT recipients generally have an overall lower risk of invasive fungal infection than do allogeneic BMT recipients, most autologous BMT recipients do not require routine anti-yeast prophylaxis **[DIII]**. However, experts recommend giving anti-yeast prophylaxis to a subgroup of autologous BMT recipients with underlying hematologic malignancies such as lymphoma or leukemia, and who have or will have prolonged neutropenia and mucosal damage from intense conditioning regimens or graft manipulation, or have recently received fludarabine or 2-chlorodeoxyadenosine (2-CDA) **[BIII]**.

E. Pediatric Note

Recommendations for preventing invasive yeast infections in pediatric and adult BMT recipients are the same, except that appropriate dose adjustments for prophylactic drugs should be made for pediatric BMT recipients. (See *Dosing Chart*).

III. Molds

A. Prevention of Exposure

1. Nosocomial mold infections in BMT recipients result primarily from respiratory exposure to and occasionally from direct contact with fungal spores (9). In particular, ongoing hospital construction and renovation have been associated with an increased risk of nosocomial mold infection, especially aspergillosis, in severely immunocompromised patients (10,11). Therefore, whenever possible, BMT recipients who remain immunocompromised should avoid renovation/construction areas **[AIII]**. (See *Hospital Infection Control* and *Strategies for Safe Living* section *I.*)
2. When constructing new BMT units, hospital planners should ensure that rooms for BMT patients have an adequate capacity to minimize fungal spore counts through use of
   a. high efficiency air filtration, e.g., HEPA filtration (12-14) **[BIII]**;

b. directed room airflow, i.e., positive air pressure in patient rooms in relation to corridor air pressure, so that air from patient rooms flows into the corridor (15) **[BIII]**;

c. properly sealed rooms, including properly sealed windows and electrical outlets (12) **[BIII],**

d. high rates of room-air exchange, i.e., ≥ 15 air changes per hour (12,13) **[BIII]**; and

e. rigid barriers between patient-care and renovation/construction areas to prevent dust from entering patient-care areas. These barriers (e.g., sealed plastic, etc.), should be impermeable to *Aspergillus* spp. (10,14) **[BIII]**. (See *Hospital Infection Control* section *X*.)

3. BMT units should be cleaned with care, especially after hospital renovation/construction, to avoid exposing BMT recipients and candidates to mold spores (16,17) **[BIII]**. (See *Hospital Infection Control* section *XI.*)

4. Some experts have reported that marijuana smoking may be associated with development of invasive pulmonary aspergillosis in immunocompromised persons, including BMT recipients (18-21). Therefore, BMT recipients should refrain from smoking marijuana to avoid *Aspergillus* spp. exposure (18, 22-26) **[DIII]**.

B. Prevention of Disease

1. Since no regimen has been shown to be clearly effective or superior in preventing aspergillosis, no recommendation for an aspergillosis prophylaxis regimen can be made at this time. Further studies are needed to determine the optimal strategy for aspergillosis prevention. Moderate dose (0.5 mg/kg/day) amphotericin B (27-30), low-dose (0.1-0.25 mg/kg/day) amphotericin B (31-33), intranasal amphotericin B spray (34), lipid formulations of amphotericin B (28,35), and aerosolized amphotericin B (36) have been suggested for aspergillosis prophylaxis, but data are limited regarding the safety and efficacy of these formulations in BMT recipients. In addition, itraconazole capsules are not recommended for fungal prophylaxis in BMT recipients (37) **[DII]** for several reasons. First, they are poorly absorbed gastrointestinally, particularly in patients who are fasting (38) or receiving cytotoxic agents

(39). Secondly, persons taking itraconazole capsules do not achieve steady-state serum levels for 2 weeks (34,40), and once achieved, these levels are lower than the average *Aspergillus* spp. mean inhibitory concentration (MIC) in BMT recipients (41). Finally, itraconazole has adverse interactions with numerous other drugs (e.g., antiepileptics, rifampin, oral hypoglycemics, protease inhibitors, vinca alkaloids, cyclosporine, methylprednisolone, and warfarin-like anti-coagulants) (42). Trials assessing the efficacy of the recently licensed cyclodextrin oral solution and intravenous formulations of itraconazole in preventing invasive fungal disease in BMT recipients are in progress; however, no recommendations regarding its use for *Aspergillus* spp. infection prophylaxis can be made at this time.

2. For BMT recipients whose respiratory specimens are culture positive for *Aspergillus* spp., acute invasive aspergillosis should be diagnosed presumptively (43) and treated pre-emptively and aggressively (e.g., with intravenous amphotericin) **[AIII]**.

C. Prevention of aspergillosis recurrence

The risk of aspergillosis recurrence has been high in allogeneic BMT recipients with pre-existing invasive aspergillosis. Previously, allogeneic BMTs were generally avoided in persons with uncontrolled, proven aspergillosis. However, a few transplant centers have recently reported successful allogeneic and autologous BMT in a small number of persons who have had successfully treated, prior invasive pulmonary aspergillosis (44-46). Due to limited data, no recommendations regarding strategies for prevention of aspergillosis recurrence can be made at this time.

IV. Other

Pneumocystis carinii. See Protozoa and Helminths section I.

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PROTOZOAL AND HELMINTHIC INFECTIONS

I. *Pneumocystis carinii*

A. Prevention of Exposure

Cases of possible person-to-person transmission of *Pneumocystis carinii* (PCP) have been reported (1-6), and use of isolation precautions in hospitals with numerous PCP patients has been shown to reduce the incidence of nosocomial PCP transmission (5). In general, standard precautions should be used for patients with PCP (6a) **[BIII]**, but some experts recommend that patients with PCP be isolated (1,4) using contact precautions if there is evidence of person-to-person transmission in the institution **[CIII]**. This subject remains controversial, and until further data are available, it may be prudent for BMT recipients to avoid exposure to persons with PCP (6a) **[BIII]**.

B. Prevention of Disease

1. Clinicians should prescribe PCP prophylaxis in allogeneic BMT recipients throughout *all* periods of immunocompromise (7). Prophylaxis should be given from engraftment until 6 months post-BMT **[AII]** for all patients, and beyond 6 months post-BMT for the *duration of immunosuppression for those who* a) are receiving immunosuppressive therapy (e.g. prednisone or cyclosporine) **[AI]** or b) have chronic graft-versus-host disease (GVHD) **[BII]**.
2. Some experts recommend an additional 1-to 2-week course of PCP prophylaxis prior to BMT (i.e., day -14 to day -2) **[CIII]**.
3. The drug of choice for PCP prophylaxis is trimethoprim-sulfamethoxazole (TMP-SMZ) **[AII]**. However, TMP-SMZ-associated myelosuppression may delay engraftment, and patients may develop sensitivity to the drug. Every effort should be made to keep such patients on the drug, including consideration of desensitization therapy, although data on this technique in BMT recipients are limited. For patients who cannot tolerate TMP-SMZ, physicians may choose to use alternative PCP prophylaxis regimens such as dapsone (8) **[BIII.** Use of aerosolized pentamidine (10) is associated with the lowest PCP prevention rates and should only be used if other agents cannot be tolerated. Atovaquone has been

suggested as an alternative drug for PCP prophylaxis in dapsone-intolerant persons with HIV-infection (10a). However, no recommendation regarding use of atovaquone in BMT recipients can be made due to lack of data.

4. Although data are limited, concomitant use of leucovorin (folinic acid) and TMP-SMZ is not recommended (11,12) **[DIII]**.
5. A history of PCP in a patient should not be considered a contraindication to BMT (13) **[DIII]**.

C. Prevention of Disease Recurrence

1. Recurrent PCP in BMT recipients is rare. However, patients with continued immunosuppression should remain on PCP prophylaxis until their immuno-suppression is resolved **[AI]**.
2. The regimen recommended to prevent toxoplasmosis recurrence in BMT recipients (TMP-SMZ) will also prevent PCP recurrence. (See *T. gondii* section B. 2.).

D. Autologous BMT Recipients

PCP prophylaxis should be considered for autologous BMT recipients who have under-lying hematologic malignancies such as lymphoma or leukemia, are receiving intense conditioning regimens or graft manipulation, or have recently received fludarabine or 2-chlorodeoxyadenosine (2-CDA) (7,14) **[BIII]**. PCP prophylaxis should be given at least 6 months post-BMT, or longer if significant immunosuppression or immuno-suppressive therapy (e.g., steroids) persists **[CIII]**. The use of PCP prophylaxis in other autologous BMT recipients is controversial **[CIII]**.

E. Pediatric Note

In general, indications for PCP prophylaxis are the same in children and adults, but pediatric doses should be used. (See *Dosing Chart*).

II. *Toxoplasma gondii*

A. Prevention of Exposure

All BMT recipients should be provided information on strategies to reduce their risk of *Toxoplasma* spp. exposure. (See *Strategies for Safe Living Following Transplantation*,

section *II*).

B. Prevention of Disease and Disease Recurrence

1. Some experts recommend that candidates for allogeneic BMT be tested for IgG antibody to determine whether they are at risk for disease reactivation post-BMT (15-17)**[CIII]** because most toxoplasmosis occurring in BMT recipients is due to recurrent disease. Such testing is controversial, however, because some patients who were seronegative for *T. gondii* pre-transplant have developed the infection post-transplant.
2. Some experts recommend toxoplasmosis prophylaxis for seropositive allogeneic BMT recipients with active GVHD or a prior history of toxoplasmic chorioretinitis (18,19), but data demonstrating efficacy are limited **[CIII]**.The optimal prophylactic regimen for toxoplasmosis in BMT recipients has not been determined, but a suggested regimen is TMP-SMZ **[BII],** although allogeneic BMT recipients have developed break-through clinical disease despite TMP-SMZ prophylaxis (15). (See *Dosing Chart*).
3. Therefore, following definitive therapy for toxoplasmosis, BMT recipients should continue receiving suppressive doses of TMP-SMZ or an alternate suggested regimen for the duration of their immunosuppression **[BIII]**. (See *Dosing Chart*).

C. Autologous BMT Recipients

Recipients of autologous transplants are at negligible risk of toxoplasmosis reactivation (15). No prophylaxis or screening for toxoplasmosis infection is recommended for such patients **[DIII]**.

D. Pediatric Note

Indications for toxoplasmosis prophylaxis are the same in children and adults, but pediatric doses should be used. (See *Dosing Chart*).

III. *Strongyloides stercoralis*

A. Prevention of Exposure

1. Allogeneic BMT recipients should avoid contact with outhouses and cutaneous

exposure to soil or other surfaces which may be contaminated with human feces (20) **[AIII]**.

2. Allogeneic BMT recipients who work in settings (e.g., hospitals, institutions) where they may be exposed to fecal matter should wear gloves when working with patients or in areas with potential fecal contamination **[AIII]**.

B. Prevention of Disease

1. A travel and residence history should be obtained for all patients prior to BMT to determine any exposures to high risk areas, (e.g., moist temperate areas such as the tropics, subtropics, parts of the Southeastern United States, and Europe) (20)**[BIII]**.
2. BMT candidates who have unexplained peripheral eosinophilia or who have resided in or traveled to areas endemic for strongyloidiasis, even in the distant past, should be screened for asymptomatic strongyloidiasis before BMT **[BIII]**. Serologic testing with an ELISA is the preferred screening method and has a sensitivity and specificity each exceeding 90% (20, 21) **[BIII]**. Although stool examinations for strongyloidiasis are specific, the sensitivity obtained from three or more stool examinations is only 60%-70% and that obtained from concentrated stool exams is, at best, 80% (20). Three or more stool examinations should be performed if serologic tests are unavailable or if strongyloidiasis is clinically suspected in a seronegative patient **[BIII]**.
3. BMT candidates whose pre-BMT screening tests are positive for *Strongyloides* spp., and those with an unexplained eosinophilia and a compelling travel or residence history suggestive of exposure to *Strongyloides stercoralis* should be empirically treated *before transplantation* (22, 23), preferably with ivermectin **[BIII]**, even if seronegative or stool negative. (See *Dosing Chart*).

C. Prevention of Disease Recurrence

1. Data are insufficient to recommend a drug prophylaxis regimen to prevent recurrence of strongyloidiasis in BMT recipients.
2. BMT recipients who had strongyloidiasis before or after BMT should be monitored carefully for signs and symptoms of recurrent infection for 6 months after

treatment **[BIII]**.

3. To prevent recurrence in patients with parasitologically confirmed strongyloidiasis, parasitologic cure following therapy should be verified with at least three consecutive negative stool examinations before proceeding with transplantation **[AIII]**.

D. Autologous BMT Recipients

Hyperinfection strongyloidiasis has not been reported following autologous bone marrow transplantation. However, the same screening precautions should be used in autologous BMT recipients **[BIII]**.

E. Pediatric Note

Indications for empiric treatment for strongyloidiasis pre-BMT are the same in children and adults except for children weighing < 15 kg, for whom the preferred drug is thiabendazole **[BIII]**. (See *Dosing Chart*).

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HOSPITAL INFECTION CONTROL

I. Room Ventilation

A. BMT units should follow published guidelines for hospital room design and ventilation (1,2) **[BIII]**.

B. All allogeneic BMT recipients should be placed in rooms with at least 15 air exchanges per hour and point-of-use high-efficiency (> 99%) particulate air (HEPA) filters that are capable of removing particles ≥ 0.3 μm in diameter (1,3) **[AIII]**. This is particularly important in hospitals and clinics with ongoing construction and renovation (4). (See section *X*.) Portable HEPA filters must be placed centrally in patient rooms so that there is space around all surfaces to allow free circulation of air **[BIII]**.

C. The need for environmental HEPA filtration for autologous BMT recipients has not been established. However, the use of HEPA-filtered rooms should be considered for autologous BMT recipients if they develop prolonged neutropenia, the major risk factor for nosocomial aspergillosis **[CIII]**.

D. A laminar air flow (LAF) room contains filtered air which moves in parallel, unidirectional flow so that the air enters the room from one wall and exits the room on the opposite wall. LAF helps to prevent bacterial contamination in the room. LAF is often used in combination with HEPA air filtration and patient decontamination. Although LAF has been shown to be effective in protecting patients from infection during aspergillosis outbreaks related to hospital construction (6,7), the value of routine LAF room use for all BMT recipients is doubtful because significant overall survival benefit has not been shown (8). BMT centers need not construct LAF rooms for each and every BMT recipient, but any BMT recipient may use LAF rooms if available **[CII]**. However, LAF rooms are preferred for allogeneic BMT recipients with aplastic anemia and HLA- identical sibling donors because LAF rooms have been associated with decreased mortality in this subgroup (9) **[BII]**.

E. Hospital rooms for BMT recipients should have positive room-air pressure when compared to any adjoining hallways, toilets, and anterooms. Anterooms should have positive pressure when compared to hallways (5). The hospital rooms should have directed airflow so that air intake occurs at one side of the room and the air is exhausted at the opposite side of the room

(1) **[BIII]**. Each hospital room should also be well-sealed, (e.g, around windows and electrical outlets) (1) **[BIII]**.

F. Infection control personnel should work with maintenance personnel to develop protocols to protect BMT units at all times from "bursts" of mold spores which may occur when air handling systems are restarted after routine maintenance shut-downs **[BIII]**.

G. For recommendations on ventilation during hospital construction/renovation projects, see section *X*.

II. Isolation and Barrier Precautions, and Hand washing

BMT units should follow published guidelines for hospital isolation practices including CDC guidelines for the prevention of nosocomial infections (10-12, 50a) **[AIII]**. However, the efficacy of specific isolation and barrier precautions in preventing nosocomial infections in BMT recipients has not been evaluated. (For recommendations on isolation and barrier precautions during construction, see section *X.)*

A. Isolation

1. BMT recipients should be placed in private (single patient) rooms **[BIII]**.
2. If contact with body fluids is anticipated, standard precautions should be followed **[BIII]**. This includes hand washing and wearing appropriate gloves, surgical masks or eye/face protection, and wearing gowns during procedures and activities that are likely to generate splashes or sprays of blood, body fluids, secretions, or excretions or cause soiling of clothing (10). When indicated, BMT recipients should also be placed on airborne, droplet, or contact precautions in addition to standard precautions (10) **[BIII]**. Careful observation of isolation precautions is important to prevent transmission of infectious agents from the health care workers, visitors, and other patients. For example, BMT patients who are known to be excreting CMV should be placed under standard precautions for the duration of CMV excretion to avoid possible transmission to CMV-seronegative BMT recipients and candidates **[AIII]**. Clinicians are cautioned that CMV excretion may be episodic and/or prolonged.

3. Some experts recommend that BMT recipients wear surgical mask and gloves when exiting their hospital rooms before engraftment **[CIII]**. (See sections *X*. and *XI.)*
4. All BMT recipients who are immunocompromised (Phases I-III of immune recovery) and candidates undergoing conditioning therapy should minimize the time spent in crowded areas of the hospital, such as waiting areas and elevators **[BIII]**. (See section *XI.*)

B. Hand washing

*Hand washing is the **SINGLE** most important and effective procedure for preventing nosocomial infection.* All persons and especially HCWs should wash their hands before entering and after leaving the rooms of BMT recipients and candidates undergoing conditioning therapy (10,11,13) or before and after any direct contact with patients **[AI]**. If gloves are worn, HCWs should put them on in the patient's room after hand washing and then discard them in the same patient's room before washing hands again on exiting the room. When worn, gloves should always be changed between patients **[AIII]**. Appropriate gloves should be used by all persons when handling potentially HSV-contaminated biological materials **[AII]**. Although handwashing with an antimicrobial soap and water is preferred, hygienic hand rubs may be used as adjuncts **[CII]**, not replacements (13a, 13b).

III. Equipment

A. All BMT units should sterilize or disinfect and maintain equipment and devices as directed by established guidelines (1,2,14) **[AIII]**.

B. BMT centers should monitor opened and unopened wound dressing supplies such as adhesive bandages (15,16) and surgical and elastic adhesive tape (17), to prevent mold contamination and subsequent cutaneous transmission to patients **[BII]**. Monitoring should consist discarding all out-dated bandages and wound dressings, and all that have damaged packaging or visual contamination [BIII]. When arm boards are used to provide support for intravenous lines, only sterile dressing materials should be used (18) and arm boards should be changed frequently (e.g., daily) **[BIII]**. In addition, unsterile

tongue depressors inserted into a piece of foam tubing should not be used as splints for intravenous and arterial catheter sites, since these have been associated with an outbreak of fatal invasive nosocomial *Rhizopus microsporus* in preterm (i.e., very low birth-weight) infants (19) **[BII]**.

C. BMT centers should not install carpeting in hallways outside patient rooms **[DII]** or in the patient rooms **[DIII]** because contaminated carpeting has been associated with outbreaks of aspergillosis in BMT recipients (20,21).

IV. Plants and Play Areas

A. Although to date, exposure to plants and flowers has not been conclusively shown to be the cause of fungal infections in BMT recipients, most experts strongly recommend that plants and dried or fresh flowers should not be allowed in the rooms of hospitalized BMT candidates undergoing conditioning therapy and BMT recipients (Phases I-III of immune recovery) because *Aspergillus* spp. have been isolated from the soil of potted ornamental plants (e.g., cacti), the surface of dried flower arrangements, and fresh flowers (3,22,23) **[BIII]**.

B. Play areas for pediatric BMT recipients and candidates undergoing conditioning therapy should be furnished so that they can be routinely and appropriately disinfected between patients **[BIII]**. Only toys, games, and videos that can be kept clean and disinfected should be allowed into the BMT unit **[BIII]**.

1. All BMT unit toys, games, and videos should be routinely and thoroughly washed (or wiped down) upon entering the BMT unit, and thereafter on a routine and as needed basis, using an Environmental Protection Agency (EPA)-approved disinfectant (23a) followed by a water rinse **[BIII]**. Cloth or plush toys should be machine washed or dry cleaned routinely and as needed **[BIII]**. Toys that cannot be washed or cleaned after use should be discarded **[BIII]**. Broviac dolls should be dissambled upon completion of play and washed with an EPA-approved disinfectant (23a), rinsed with tap water, and allowed to air dry before other children are allowed to play with them **[BIII]**.
2. For patients in isolation,

a) Disposable play items should be offered whenever possible **[BIII]**.

b) Before returning a washable toy used in an isolation room to the pediatric play room for use by another child, it should be cleaned again as described in B. 1. above **[BIII]**.

c) When a child is taken out of isolation, toys, games, videos, etc. used during the period of isolation and which may serve as fomites for infection should be thoroughly cleaned with an EPA-approved disinfectant (23a) **[BIII]**. Following use in isolation rooms, cloth or plush toys are to be placed in a plastic bag and separated from un-used toys. All cloth or plush toys used in isolation rooms should be machine washed or dry cleaned before being given to another child to play with **[BIII]**. Toys that cannot be washed or cleaned after use in an isolation room should be discarded **[BIII]**.

3. Water-retaining bath toys have been associated with an outbreak of *Pseudomonas aeruginosa* in a pediatric oncology ward (24); therefore, these toys should not be used by immunocompromised BMT recipients and candidates **[DII]**.

V. Health-care Workers

A. Each hospital or BMT center should prepare a written comprehensive policy on the immunization of hospital personnel that meets current CDC and Advisory Committee on Immunization Practices (ACIP) recommendations (25) **[BIII]**. Such immunizations are needed to prevent transmission of vaccine-preventable diseases to BMT recipients and candidates undergoing conditioning therapy.

B. All HCWs with diseases transmissible by air, droplet, and direct contact (e.g., VZV, infectious gastroenteritis, HSV lesions of lips or fingers and URIs such as RSV, and influenza virus) should be restricted from patient contact and temporarily reassigned to other duties **[AI]**. (See section XI. F.) BMT units should follow published recommendations regarding duration of work restrictions for HCWs with infectious diseases (26-28) **[BIII]**. In contrast, BMT unit HCWs with sexually transmitted or blood-borne infections such as HIV or hepatitis B or C viruses should not be restricted from patient contact **[DIII]** as long as they do not perform exposure-prone invasive procedures such as oral, cardiothoracic, colorectal and

obstetric/gynecologic procedures (27, 29). HCWs with acute or chronic hepatitis B e antigenemia or HIV infection who wish to perform exposure-prone invasive procedures should consult state regulations and obtain approval from an expert review panel (27) **[BIII]**.

C. Work exclusion policies should be designed to encourage HCWs to report their illnesses or exposures **[AII]**.

VI. Visitors

A. Hospitals should have written policies for screening BMT unit visitors, especially children, for potentially infectious conditions. Such screening should be performed by clinically trained health care personnel **[BII]**.

B. Visitors who have communicable infectious diseases such as a URI, a flu-like illness, recent exposure to communicable diseases, an active shingles rash whether covered or not, a VZV-like rash within 6 weeks of receiving a live attenuated VZV vaccine, or a history of receiving an OPV within the previous 3-6 weeks should not be allowed in the BMT unit or to have direct contact with BMT recipients or BMT candidates undergoing conditioning therapy **[AII]**.

C. There is no absolute minimum age requirement for BMT unit visitors. However, any visitor must be able to understand and follow appropriate hand washing and isolation precautions **[AIII]**.

D. The number of BMT unit visitors at any one time should be restricted to a number that permits the nursing staff to perform appropriate screening for contagious diseases and adequate instruction and supervision of hand washing, glove and mask use, and biosafety precautions **[BIII]**. (See section *II.*)

VII. Patient Skin and Oral Care

A. To optimize skin care, BMT recipients should receive daily baths or showers both during and after transplantation **[BIII]**. A mild soap should be used for washing BMT patient's skin **[BIII]**. Skin care during neutropenia should also include daily inspection of skin sites likely to be portals of infection, such as the perineum and intravascular access sites **[BIII]**.

B. BMT recipients and candidates undergoing conditioning therapy should maintain good perineal hygiene to minimize loss of skin integrity and risk of infection **[BIII]**. To facilitate this, BMT units are advised to develop special protocols for patient perineal care. Protocols should include recommendations for gentle but thorough perineal cleaning after each bowel movement, and for thorough drying of the perineum after each urination for all BMT recipients **[BIII]**. Females should always wipe the perineum from front to back after using the toilet to prevent fecal contamination of the urethra and urinary tract infections **[AIII]**. Moreover, to prevent vaginal irritation, menstruating immunocompromised BMT recipients should not use tampons **[DIII]** to avoid the risk of cervical and vaginal abrasions. In addition, the use of rectal thermometers, enemas, suppositories, and rectal exams are contraindicated in BMT recipients to avoid skin or mucosal breakdown **[DIII]**.

C. All BMT candidates should receive a dental consult to assess their oral health, perform any needed treatment, and allow oral healing before conditioning therapy begins to reduce their risk of oral infections post-transplant (30) **[AIII]**. Likely sources of dental infection should be vigorously eliminated **[AIII]** (e.g., moderate to deep decay, and extraction of teeth with pockets 8 mm or deeper). Establishment of the best possible periodontal health pre-BMT is one of the most important steps to avoid short-and long-term oral infections. BMT recipients with mucositis and candidates undergoing conditioning therapy should maintain good oral hygiene by performing oral rinses 4-6 times daily with sterile water, normal saline, or sodium bicarbonate solutions (30) **[AIII]**. In addition, teeth should be brushed with or without toothpaste at least twice daily with a soft regular toothbrush (30) **[BIII]**. If the patient cannot tolerate these brushings, use of sponge or foam tooth-brushes, or “supersoft” toothbrushes may be used **[CIII]** but clinicians should be aware that these are less desirable than soft regular toothbrushes because they remove less dental debris (30). BMT recipients and candidates undergoing conditioning therapy who are skilled at dental flossing should floss daily if flossing can be done atraumatically **[BIII]**. To decrease the risk of mucosal irritation and infection, fixed orthodontic appliances and space maintainers should not be worn from the

start of conditioning therapy until resolution of mucositis, or throughout any subsequent periods of mucositis (30) **[DIII]**.

VIII. Prevention of Bacterial Intravascular Catheter-related Infections

A. BMT units are advised to implement published guidelines for preventing intravascular device-related infections (31) **[BIII]**.

B. For long-term central venous access in children, BMT providers may consider the use of a totally implantable device in children < 4 years of age if the anticipated duration of vascular access is > 30 days **[CII]**. However, such a device in children < 4 years of age is not generally used as the actual BMT infusion site because a) problems with skin fragility contraindicate repeated punctures over the port site and b) the port device may have an insufficient number of lumens for optimal patient management immediately post-BMT.

C. No recommendation regarding the use of antibiotic-impregnated central venous catheters in BMT recipients can be made due to lack of data.

IX. Infection Control Surveillance

A. BMT units are advised to follow standard guidelines for surveillance of antimicrobial use and nosocomial pathogens and their susceptibility patterns (32) **[BIII]**.

B. BMT centers should **not** perform routine periodic fungal (33,34) or bacterial cultures of asymptomatic BMT recipients **[DII]**.

C. In the absence of epidemiologic clusters of infections, BMT centers should **not** perform routine periodic bacterial surveillance cultures of the BMT center environment, or of equipment or devices used for respiratory therapy, pulmonary-function testing, or delivery of inhalation anesthesia (1) **[DIII]**. Furthermore, BMT centers need not perform routine fungal cultures of devices and dust in the rooms of BMT recipients and candidates undergoing conditioning therapy **[DIII]**. However, some experts have suggested that hospitals perform routine sampling of air, ceiling tiles, ventilation ducts, and filters to test for molds, especially when construction or renovation is occurring near or around the rooms of immuno-compromised patients (22, 33), or when clinical surveillance demonstrates a possible increase

in aspergillosis cases **[CIII]**. Strategies which may decrease fungal spores in the ventilation system include eliminating access of birds (primarily pigeons) to air-intake systems, removing bird droppings from the air-intake ducts, and eliminating moss from the hospital roof (22).

D. BMT units should routinely perform surveillance for the number of aspergillosis cases occurring in BMT recipients, especially during hospital construction/renovation **[BIII]**. A two-fold or greater increase in the incidence of aspergillosis over any 6-month period indicates that the BMT unit environment should be evaluated for breaks in infection control techniques and procedures and that the ventilation system, in particular, should be carefully investigated (22) **[BIII]**.

X. Construction/renovation and building cleaning

Hospital construction and renovation has been associated with an increased risk of nosocomial fungal infection, especially aspergillosis, in severely immunocompromised patients (35, 36). (See *Fungal Infections* section.)

A. Whenever possible, BMT recipients who remain immunosuppressed should avoid construction/renovation areas **[AIII]**. Immunosuppressed BMT recipients are defined as those who are < 24 months post-BMT, or are on immunosuppressive therapy, or have graft-versus-host disease (GVHD).

B. When planning for construction/renovation, the BMT center should include plans for intensified aspergillosis-control measures **[BIII]**. The construction/renovation infection-control planning committee should include engineers, architects, housekeeping staff, and infection control personnel (37) **[BIII]**.

C. When constructing new BMT units, hospitals should ensure that patient rooms in the new BMT center have adequate capacity to minimize fungal spore counts by following room ventilation recommendations. (See section I.). In addition, to protect BMT patient care areas during fire emergencies, weather stripping should be placed around stairwell doors, or alternatively, the stairwell air should be filtered to the level of safety of the adjacent hospital air **[BIII]**.

D. When a new hospital building is constructed, the cooling tower(s) should be placed so

that the tower aerosol drift is directed away from the hospital's air intake system and the volume of aerosol drift is minimized (1) **[BIII]**.

E. During hospital construction/renovation, hospitals should construct sealed barriers between patient-care and construction/renovation areas to prevent dust from entering patient-care areas. These barriers (i.e., sealed plastic) should be impermeable to *Aspergillus* spp. (4, 35) **[BIII]**. Some experts prefer that the barriers consist of sheet-rock walls extending from the floor to slab ceiling instead of taped plastic drapes (36) **[CIII]**. If impervious barriers cannot be created around the construction/renovation area, patients should be moved from the area until renovation/construction is complete and the area has been cleaned appropriately (36) **[BIII]**. (See sections *K, L,* and *M* below).

F. Hospital construction/renovation areas should have negative air pressure relative to that in adjacent patient-care areas, if there are no contraindications for such pressure differential, such as nearby patients with infectious tuberculosis (4,36) **[BIII]**. Ideally, air from the construction/renovation areas should be exhausted to outside of the hospital (36) **[CIII]**.

G. During hospital construction/renovation, BMT units should direct pedestrian traffic occurring near construction/renovation areas *away* from patient-care areas to limit opening and closing of doors (or other barriers) that may cause dust dispersion, entry of contaminated air, or tracking of dust into patient areas, especially those in the BMT unit (36) **[BIII]**. A side elevator to which patients do not have access should be dedicated to construction-use only. Construction workers, whose clothing may be contaminated with *Aspergillus* spp. spores, should use the construction elevator and avoid contact with patients, patient care areas and other elevators **[BIII]**.

H. Some experts recommend that BMT recipients wear the N95 respirator (38, 39) to prevent mold exposure while being transported near hospital construction/renovation areas **[BIII]** because the N95 respirators are considered to be effective against any aerosol. However, no commercially available respirator has been tested specifically for its efficacy in reducing exposure to mold spores (i.e., *Aspergillus* spp.) in hospital

construction/renovation areas. To be maximally effective, N95 respirators must be fit-tested and all respirator users must be trained in their proper use. With proper fit-testing and training, N95 respirators reliably reduce aerosol exposure by 90%. Without fit-testing and training, aerosol exposure would be reduced but not necessarily by 90%. For patients who cannot use or tolerate a N95 respirator, some experts have suggested using the reusable Powered Air Purifying Respirator (PAPR) (38, 39) which can be used for patients in wheelchairs. However, limitations of the PAPR include its cost and that it is not appropriate for young children and infants. Standard surgical masks provide negligible protection against mold spores and are not recommended for this indication **[DIII]**.

I. For information on conducting infectious disease surveillance during construction, see section *IX*.

J. Newly constructed areas should be cleaned *before* patients are allowed to enter them (36) **[BIII]**. Decontamination should be done using copper-8-quinolate (4) **[BIII]**. Also, areas above false ceilings located under or adjacent to construction areas should be vacuumed (22) **[BIII]**.

K. BMT units should prohibit exposures of patients to activities such as vacuuming or other floor or carpet cleaning that may cause aerosolization of *Aspergillus spp*. spores **[AIII]**. Accordingly, doors to patient rooms should be closed when vacuuming BMT unit corridors. All vacuum cleaners used in the BMT unit should be fitted with HEPA filters. In addition, a 1:100 solution of household bleach (or other EPA-approved agent for the disinfection of inanimate objects) (23a) should be used when wet vacuuming is performed in the BMT unit **[BIII]**.

L. Water leaks should be cleaned up and repaired as soon as possible but at least within 72 hours to prevent mold proliferation in floor and wall coverings, ceiling tiles, and cabinetry, etc., in and around all BMT patients care areas **[BIII]**. If cleanup and repair are delayed until >72 hours after the water leak, the involved materials should be assumed to contain fungi and handled accordingly.

M. Flooring and finishes (i.e., wall coverings, window shades, countertops) chosen for use in BMT units must be scrubbable, easily cleaned, and collect minimal dust **[BIII]**.

XI. Control of Specific Nosocomial Infections

A. *Legionella* spp.

1. BMT clinicians should always consider Legionnaire's disease (LD) in the differential diagnosis of pneumonia in a BMT recipient (1) **[AIII]**. Appropriate tests to confirm LD include culturing sputum, BAL, and tissue specimens, testing BAL specimens for legionellae by direct fluorescent antibody (DFA), and testing urine for legionellosis urine antigen.
2. When a case of definite or possible laboratory-confirmed nosocomial LD is identified, the BMT unit should:
   a. Report the case(s) to the local or state health department if the disease is reportable in the state or if assistance is needed (1) **[AIII]**.
   b. In consultation with the hospital infection control team, conduct a thorough epidemiologic and environmental investigation to determine the likely environmental source(s) of *Legionella* spp. such as showers, tap water faucets, cooling towers, hot water tanks, and carpet cleaner water tanks (39a, 39b)**[BI]**. The source of legionella infection should be identified, decontaminated, and/or removed.
3. Because BMT recipients are at much higher risk for disease and death from legionellosis compared to most other hospitalized persons (39a), periodic routine culturing for legionellae from the unit's potable water supply may be considered part of an overall strategy to prevent Legionnaire's disease in transplant units **[CIII]**. The optimal methodology (frequency, number of sites) for environmental surveillance in transplant units has not been determined. Because BMT recipients are at high risk of Legionnaire's disease and there are no data to determine a "safe" concentration of legionellae organisms in potable water, the goal of environmental surveillance for legionellae should be to maintain water systems with no detectable organisms **[AIII]**. Clinicians must maintain a high index of suspicion for legionellosis in transplant patients with nosocomial pneumonia even when environmental surveillance cultures do not yield legionellae **[AIII]**.
4. If *Legionella* spp. are detected in water supplying a BMT unit or clinic, the following steps should be taken until *Legionella* spp. are no longer detected by culture:

a. The water supply should be decontaminated (1) **[AII]**.

Until the water supply is decontaminated,

b. BMT recipients should be given sponge baths from water which is not contaminated with *Legionella* spp. (e.g., not from the BMT unit's *Legionella* spp. contaminated potable water system) **[BIII]**. Patients should not take showers in LD-contaminated water **[DIII]**.

c. Water from faucets containing LD-contaminated water should not be used in the patient rooms or the BMT unit and outpatient clinic to avoid creating infectious aerosols **[CIII]**.

d. BMT recipients should be given sterile water instead of tap water for consumption, tooth brushing, or flushing nasogastric tubes during Legionellosis outbreaks to prevent possible exposure to Legionella-contaminated aerosols **[BIII]**.

5. BMT units and clinics should use only sterile water (not distilled unsterile water) for rinsing nebulization devices and other semicritical respiratory-care equipment after cleaning and/or disinfection and for filling reservoirs of nebulization devices (1)**[BII]**.
6. BMT units and clinics should **not** use large volume room-air humidifiers that create aerosols (e.g., by Venturi principle, ultrasound, or spinning disk) and thus are actually nebulizers (1) **[DI]**. However, these humidifier/nebulizers can be used if they are sterilized or subjected to daily high-level disinfection and filled only with sterile water (1) **[CIII]**.
7. When a new hospital with a BMT unit is constructed, the cooling tower(s) should be designed and constructed so that the tower drift is directed away from the hospital's air intake system and the volume of aerosol drift is minimized (1)[BI].
8. For operational hospital cooling towers, hospitals should (1)**[BII]**
   a. install drift eliminators,
   b. regularly use an effective biocide,
   c. maintain towers according to the manufacturer's recommendations,
   d. keep adequate maintenance records.
9. BMT clinicians are encouraged to consult published recommendations on the

prevention of nosocomial legionellosis (1, 40) **[BIII]**.

B. Methicillin-Resistant *Staphylococcus aureus* (MRSA)

1. HCWs in BMT units should follow basic infection control tenets such as hand washing between patients and use of barrier precautions essential for MRSA control **[AII]**. If MRSA is a substantial problem within the BMT unit and there is evidence of ongoing MRSA transmission, MRSA infected patients should be cohorted (e.g., cared for exclusively by a small number of HCWs) **[BIII]**.
2. BMT transplant recipients with recurrent *S. aureus* infections should undergo extensive evaluation for persistent colonization, including cultures of nares, groin, axilla, and ostomy sites (e.g., tracheostomy, G-tube) **[BIII]**. For patients with recurrent MRSA infection, the carrier state should be eradicated with mupirocin calcium ointment, 2% applied to the nares. Incorrect or over-use of mupirocin may select for mupirocin-resistant *S. aureus*. For patients who fail mupiricin, some groups have used bacitracin, TMP-SMZ, or rifampin given with another antibiotic, but no standardized protocol using these drugs for this indication has been evaluated and no recommendations can be made due to lack of data. *See Dosing Chart.* Selection of a systemic antibiotic should be guided by susceptibility patterns.
3. Intravascular cannulas or other implantable devices that are infected or colonized with MRSA should be removed **[AIII]**.
4. Patients with MRSA should be placed under contact precautions until all antibiotics are discontinued and repeated cultures are negative (50a) **[BIII]**.

C. *Staphylococcus* spp. with reduced susceptibility to vancomycin

1. All BMT centers should have sufficient laboratory capability to identify all *Staphylococcus* spp. isolates and their susceptibility patterns to antibiotics, including vancomycin (41, 42) **[AIII]**. In addition, all BMT centers should conduct routine surveillance of patient isolates to monitor for the emergence of *Staphylococcus* spp. strains with reduced susceptibility to vancomycin (42, 43) **[AIII]**.
2. Reduced susceptibility should be considered for all *S. aureus* strains which have a vancomycin minimum inhibitory concentration (MIC) of $\geq 4 \mu$g/mL and all

coagulase-negative staphylococci which have a vancomycin MIC of ≥8 μg/mL. If repeat testing of the organism in pure culture confirms the genus, species, and elevated vancomycin MICs, the following steps should be taken (44):

a. The laboratory should immediately contact the hospital infection control personnel, the patient's clinical unit, and the patient's attending physician, as well as the local or state health department and CDC's Hospital Infections Program, telephone (404) 639-6400 (41, 42, 44, 45) **[AIII]**.
b. The BMT center's infection control personnel, in collaboration with appropriate authorities (i.e., state and local health departments and CDC) should promptly initiate an epidemiologic and laboratory investigation (44, 45) **[AIII]** and follow published guidelines for the control of such species (42, 44, 45) **[BIII]**.
c. Medical and nursing staff should institute contact precautions (gown, gloves, antibacterial soap for hand washing, and wear masks when there is likely contamination of the HCW with secretions such as suctioning the respiratory tract) as recommended for multidrug-resistant organisms (10, 41, 44), minimize the number of persons with access to colonized/infected patients (44), and cohort colonized/infected patients (e.g., they should be cared for exclusively by a small number of HCWs)(43, 44) **[AIII]**.
d. If a patient in a BMT unit or clinic is colonized or infected with staphylococci that have reduced susceptibility to vancomycin,

3. Avoiding overuse and misuse of antibiotics will decrease the emergence of *Staphylococcus* spp. with reduced susceptibility to vancomycin (43, 44). Therefore, medical and ancillary staff members who are responsible for monitoring antimicrobial use patterns in the facility should routinely review vancomycin-use patterns (41, 42, 44) **[AIII]**. In addition, BMT centers should vigorously institute prudent use of all antibiotics, especially vancomycin, to prevent the emergence of *Staphylococcus* spp. with reduced susceptibility to vancomycin (41, 42, 44-46) **[AII]**.
4. Intravascular cannulas or other implantable devices that are infected or colonized with *Staphylococcus* spp. strains with reduced susceptibility to vancomycin should

be removed **[AIII]**.

D. Vancomycin-resistant enterococci (VRE)

1. Use of intravenous vancomycin is associated with VRE emergence. Vancomycin and all other antibiotics, especially anti-anaerobic agents such as metronidazole, and third generation cephalosporins, must be used judiciously (41, 47, 48) **[AII]**. Oral vancomycin use may be limited by treating recurrences of *Clostridium difficile* diarrhea with oral metronidazole instead of vancomycin **[BIII]**.
2. Some experts recommend placing patients with a history of VRE or VRE colonization into "permanent" isolation, during both clinic visits and hospitalizations **[CIII]**.
3. To control VRE exposure, strict attention should be paid to standard infection control measures **[AI]**, such as:
    a) hand washing with antibacterial soap before entering and after leaving BMT recipients' rooms, especially those who have VRE colonization or infection
    b) whenever possible, cohorting patients who are known to be colonized or infected with VRE (47).
    c) following appropriate disinfection of patient rooms and equipment (48, 49).
    d) placing patients with VRE under contact precautions until all antibiotics are discontinued and repeated cultures are negative (50a). HCWs should always wear gloves when in the VRE patient or carrier's room, and discard gloves in the patient's room before exiting.
4. There is no evidence that treating VRE carriers is beneficial. Therefore, chronic antibiotic treatment of carriers is not recommended **[DIII]**.
5. The role of outpatient surveillance in VRE control is unknown; such surveillance is costly and should not be undertaken in a non-outbreak setting **[DIII]**.
6. A history of having resolved VRE bacteremia and/or being a VRE carrier are not contraindications to BMT **[BIII]**.
7. BMT recipients and candidates should be screened for VRE colonization at the time of interfacility transfer to allow for immediate institution of appropriate

infection control practices, and to minimize transmission of VRE between and within facilities (50b) **[BII]**.

E. *Clostridium difficile*

1. BMT clinicians should follow recommendations for controlling *C. difficile* (50) [AIII]. All patients with *C. difficile* disease should be placed under contact precautions for the duration of illness (50a) **[AII]**.
2. All HCWs who anticipate contact with a *C. difficile*-infected patient or the patient's environment or possessions should put on gloves before entering the patient's room (50-52) and before handling the patient's secreta and excreta **[AI]**.
3. During *C. difficile* outbreaks BMT centers should restrict the use of antibiotics such as clindamycin (53) **[BII]**.
4. To prevent transmission of *C. difficile* to patients during nosocomial *C. difficile* outbreaks, surface disinfection of the hospital ward environment (e.g., floors, walls, bed frames, doors, bathroom surfaces) with solutions of 1:100 dilution of household bleach (sodium hypochlorite) is recommended (23a), along with appropriate antibiotic treatment of patients with *C. difficile* disease (54) **[BII]**.
5. Some experts recommend antibiotic treatment of *C. difficile* carriers (55). However, others have shown that treatment of asymptomatic *C. difficile* carriers with metronidazole is not effective and that treatment with vancomycin is only effective temporarily (i.e., < 2 months after treatment) (56). Consequently, no recommendation regarding treatment of asymptomatic *C. difficile* carriers can be made at this time.
6. Similarly, even though symptomatic *C. difficile* disease recurrence or relapse occurs in 7%-20% of patients (50), data are insufficient to make a recommendation for prevention of multiple *C. difficile* relapses.
7. The following are **not** recommended for *C. difficile* control:
   a. Routine stool surveillance cultures for *C. difficile* for patients or HCWs even during outbreaks **[DIII]**,
   b. Culturing HCWs' hands for *C. difficile* **[DIII]**,

c. Treating patients presumptively for *C. difficile* disease pending toxin results **[DIII]**, unless the patient is very sick with a compatible syndrome and/or the hospital has a high prevalence of *C. difficile* **[CIII]**.

8. The prophylactic use of lyophilized *Saccharomyces boulardii* to reduce diarrhea in antibiotic recipients is not recommended because this therapy was not associated with a significant reduction in diarrhea associated with *C. difficile* disease (57), and has been associated with *Saccharomyces boulardii* fungemia (57a) **[DIII]**.

F. Community Respiratory Viruses infections

1. Clinicians should institute appropriate precautions and infection control measures to prevent nosocomial pneumonia in hospitalized BMT recipients and candidates undergoing conditioning therapy, especially during community or nosocomial CRV outbreaks (1)**[AIII]**. (See sections *II.*, *V.*, *VI.* , *IX.*, and the *Viral Infections* section on CRV.)

2. Patients with URI and/or LRI symptoms should be placed under contact precautions (for most viral respiratory infections), or droplet precautions (for influenza or adenovirus), or airborne precautions (for measles or varicella), to avoid transmitting infection to other BMT candidates and recipients, as well as to HCWs and visitors **[BIII]**. It is especially important for BMT recipients with RSV infection to be identified and placed under contact precautions immediately **[AIII]** to prevent nosocomial transmission. When suctioning the respiratory tract from patients with URI and/or LRI symptoms, the HCW should wear a gown and surgical mask to avoid contamination from the patient's respiratory secretions. All protective clothing (e.g., gown, glove, and surgical mask) should be put on when entering a patient's room and should be discarded in the same room before exiting, and therefore should always be changed between patient rooms (1) **[AIII]**. When caring for a BMT recipient or candidate undergoing conditioning therapy with URI and/or LRI, HCWs and visitors should change gloves and wash hands a) after contact with a patient; b) after handling respiratory secretions or objects contaminated with secretions from one patient and before contact with another patient, object, or environmental surface;

and c) between contacts with a contaminated body site and the respiratory tract of or respiratory device on the same patient (1)**[AII]**. This is important because most respiratory infections are usually transmitted by contact, especially hand to nose and eye. Therefore just wearing a surgical mask, without appropriate handwashing and glove-wearing, is insufficient to prevent transmission of CRV infections.

3. During nosocomial outbreaks, some experts recommend that BMT recipients or candidates undergoing conditioning therapy be placed under contact precautions (63)**[CIII]**.
4. Even when there is no nosocomial or community outbreak of CRV infections, all persons who enter the BMT unit should be screened daily for URI symptoms, including visitors and HCWs **[BIII]**. Some experts recommend that HCWs who work in BMT centers provide daily verification (e.g., using sign-in sheets) that they are free of URI symptoms before being allowed to provide patient care.
5. HCWs and visitors with URI symptoms should be restricted from contact with BMT recipients and BMT candidates undergoing conditioning therapy to minimize the risk of CRV transmission (63)**[AIII]**. All HCWs with URI symptoms should be restricted from patient contact and reassigned to non-patient care duties until their symptoms resolve **[BIII]**. Visitors with URI symptoms should be asked to defer their visit to the BMT center (63) until their URI symptoms resolve **[BIII]**.
6. The respiratory secretions of any hospitalized BMT candidate or recipient with signs and/or symptoms of CRV infection should be tested promptly by viral culture and rapid diagnostic tests for CRV **[BIII]**. Appropriate samples include naso-pharyngeal (NP) washes, swabs, or aspirates, throat swabs, and BAL fluid. This is important because pre-emptive treatment of some CRVs, such as influenza and RSV (57c), may prevent severe disease and death in BMT recipients.
7. Viral shedding in BMT recipients with CRV infection has been documented to last up to 4 months for influenza (59), up to 2 years for adenovirus (51,61) and up to 22 days for RSV (58); however, RSV viral shedding has been reported to last up to 112 days in a child with severe combined immunodeficiency (SCID) (58a).

Therefore, to prevent nosocomial transmission of CRV (58), BMT units should recognize that prolonged CRV shedding may occur when determining the duration of appropriate precautions for CRV infected BMT recipients or candidates undergoing conditioning therapy **[CIII]**. BMT centers should use serial testing using cultures from NP swabs, throat swabs or aspirates, or rapid antigen tests to help determine whether patients have stopped shedding influenza virus **[BIII]**.

8. Some experts recommend that BMT providers routinely conduct CRV surveillance among BMT recipients to detect outbreaks and implement infection control measures as early as possible **[CIII]**.
9. During RSV season, BMT recipients and candidates with respiratory signs and/or symptoms should be tested for RSV infection (i.e., the presence of RSV antigen in respiratory secretions tested by ELISA and viral culture) starting with admission to the BMT unit. All patients who are RSV-antigen positive should be cohorted during nosocomial RSV outbreaks because this has been shown to reduce nosocomial RSV transmission (62, 63) **[BII]**. Symptomatic HCWs should be excluded from patient contact until symptoms resolve. (See sections V. B. and C.).
10. HCWs and visitors with conjunctivitis should be restricted from direct patient contact until the drainage resolves (usually about 5-7 days for adenovirus disease) and the ophthalmology consultant concurs that inflammation has resolved (26) **[AII]** to avoid possible transmission of adenovirus to BMT recipients.
11. Preventing CRV exposure in BMT recipients after hospital discharge is more challenging due to high CRV prevalence in most communities. Preventive measures should be individualized in accordance with the immunologic status and and tolerance of the patient. (See *Strategies for Safe Living Following Transplantation* section *I.*) In outpatient waiting room settings, patients with CRV infections should be separated to the extent possible from other patients **[BIII]**.

G. *Mycobacterium tuberculosis* (TB)

1. BMT candidates should be screened for TB by a careful medical history and chart review to ascertain any history of prior TB exposure (64) **[AI]**. Also,

consideration should be given to administering a tuberculin skin test (TST) using the Mantoux method with the 5 Tuberculin Units (TU) of purified protein derivative (PPD) **[CIII];** but because of the patients' immunocompromise, it may not be reliable. If a TST is given, the Tubersol, not Aplisol, formulation should be used.

2. Persons with a recently positive TST or a history of a positive TST and no prior preventive therapy should be given a chest X-ray and evaluated for active TB (64) **[AI]**. In immunosuppressed persons, a positive TST is usually defined as ≥10 mm of induration (65), although some experts recommend that a 5 mm cutoff be used because of the decreased ability of immunosuppressed persons to mount a delayed-type hypersensitivity response (66) **[CIII]**. In addition, immunosuppressive therapy decreases the sensitivity of the TST, regardless of whether a 5 or 10 mm cutoff is used. Therefore, BMT providers should **not** rely solely on the TST to determine whether latent TB infection is present and if preventive therapy should be given to BMT recipients or candidates **[DIII]**. Instead, a full 9-month course of INH preventive therapy should be given to immunocompromised BMT recipients or candidates who have been significantly exposed to someone with active, infectious (i.e., sputum-smear positive) pulmonary or laryngeal tuberculosis, regardless of the BMT recipient's or candidate's TST status **[BIII]**. A full, 9-month course of INH preventive therapy should also be given to BMT recipients or candidates with a positive TST who were not previously treated and have no evidence of active TB disease (67) **[AII]**. (See *Dosing Chart*.) Routine anergy screening may not be reliable in BMT recipients and candidates undergoing conditioning therapy and therefore is not recommended **[DIII]**. A BMT should not be canceled or delayed because of a positive PPD **[DIII]**.
3. Use of a 2-month course of a daily pyrazinamide/rifampin (PZA/RIF) regimen has been suggested as an alternate preventive therapy in immunocompromised persons with TB (68). However, there are few data on safety and efficacy of this regimen in non-HIV infected persons. Furthermore, rifampin has significant drug inter-actions with numerous medications, including cyclosporine, tacrolimus (FK506),

corticosteroids, fluconazole, and pain medications. Therefore, routine use of the 2-month PZA/RIF prophylactic therapy regimen in BMT recipients is not recommended **[DIII]**. However, the 2-month PZA/RIF regimen may be considered in BMT *candidates* who are not at risk for serious rifampin drug interactions and whose BMT is not scheduled until at least 2 weeks after completion of the 2-month PZA/RIF course **[CIII]**. This delay will diminish the possibility of adverse effects of rifampin on drugs used for routine BMT OI prophylaxis such as fluconazole (68).

4. A BMT candidate or recipient who has been exposed to an active case of extra-pulmonary, and therefore, less infectious TB does not require preventive therapy **[DIII]**.
5. BMT units should follow guidelines regarding the control of TB in health care facilities (38, 39) including instituting airborne precautions and negative pressure rooms for patients with suspected or confirmed pulmonary or laryngeal TB (38, 50a) [AII]. HCWs should wear respirators (i.e., N95) to protect them from possible TB transmission from patients with active pulmonary or laryngeal TB, especially during cough-inducing procedures (10,38,39,71) **[AIII]**. To be maximally effective, respirators such as the N95 must be fit-tested; and all respirator users must be trained to use them properly **[AIII]**. Therefore, it is not necessary to change N95 masks between patient rooms **[DIII]**.
6. BCG vaccination is contraindicated in BMT candidates and because it may cause disseminated or fatal disease in immunocompromised persons (69, 70) **[EII]**. (See *Immunization* section.)
7. There is no identified role for chronic suppressive therapy or follow-up surveillance cultures in BMT recipients who have a history of successfully treated TB **[DIII]**.

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STRATEGIES FOR SAFE LIVING FOLLOWING TRANSPLANTATION - PREVENTION OF EXPOSURE AND DISEASE

I. Avoiding environmental exposures

BMT recipients and candidates undergoing conditioning therapy, especially allogeneic transplant recipients, and parents of pediatric BMT recipients and candidates should be educated about strategies to avoid environmental exposures to opportunistic pathogens **[AIII]**.

A. BMT recipients and candidates should wash their hands thoroughly (e.g., with soap and water) and often (e.g., before eating or preparing food, after changing diapers, after gardening or touching plants or dirt, after touching pets or animals, and after touching secreta or excreta or anything [e.g., clothing, bedding, toilets, urinals bedpans] that may have had contact with human or animal stool, after going outdoors, and before and after touching wounds) (1). Conscientious handwashing is especially important during the first 6 months post-BMT and during other periods of significant immunosuppression (e.g., GVHD, systemic steroid use, or relapse) **[BIII]**. Pediatric BMT recipients and candidates should be supervised by adults during hand washing to ensure thorough cleaning (2) **[BIII]**. Although handwashing with an antimicrobial soap and water is preferred, hygienic hand rubs may be used as adjuncts **[CII]**, not replacements (2a, 2b).

B. Sexually active BMT recipients should avoid sexual practices that may result in oral exposure to feces (2,3) **[DIII]**.

C. BMT recipients who visit or live on farms should follow published recommendations for preventing cryptosporidiosis (2,4) **[BIII]**. (For further information on pets and *Cryptosporidium*, see section *II.*)

D. To prevent CRV transmission to BMT recipients after hospital discharge, the following precautions should be observed:

1. BMT recipients should wash their hands frequently and thoroughly with soap and water, especially during CRV season **[BIII]**.
2. BMT recipients should avoid close contact with persons with respiratory illnesses **[BIII]**. When this is unavoidable, close contacts with respiratory-illnesses should

be encouraged to wash their hands frequently and to wear surgical masks or, at a minimum, smother their sneezes and coughs in disposable tissues. Alternatively, the BMT recipient may wear a surgical mask **[CIII]**.

3. BMT recipients should avoid crowded areas such as shopping malls or public elevators where close contact with persons with respiratory illnesses is likely **[BIII]**.
4. Allogeneic transplant recipients should avoid exposure to construction or excavation sites or other dust-laden environments for the first 6 months post-BMT and during other periods of significant immunosuppression (e.g., GVHD, systemic steroid use, or relapse) to avoid exposures to molds **[BIII]**. HCWs should advise outpatient BMT recipients of travel routes to the BMT clinic that will avoid or minimize exposure to construction sites **[BIII]**.
5. Coccidioidomycosis is uncommon following allogeneic BMT. However, patients traveling to or residing in coccidioidomycosis-endemic areas such as the American southwest, Mexico, and Central and South America, should avoid or minimize exposure to disturbed soil, including construction/excavation sites, areas with recent earthquakes, farms, or other rural areas **[CIII]**.
6. Smoking tobacco and exposure to environmental tobacco smoke are risk factors for bacterial and community respiratory virus infections in healthy adults and children (5-8). Consequently, it is reasonable for BMT physicians to advise BMT recipients not to smoke and to avoid exposure to environmental tobacco smoke **[CIII]**. However, there are no data which specifically assess whether smoking or environmental smoke exposure are risk factors for OIs in BMT recipients.

E. Persons whose occupations involve animal contact (e.g., veterinarians, pet store employees, farmers, or slaughterhouse workers) may be at increased risk for toxoplasmosis and other zoonotic diseases. Although data are insufficient to justify a general recommendation against BMT recipients working in such settings, these exposures should be avoided during the first 6 months post-BMT and during other periods of significant immunosuppression (e.g., GVHD, systemic steroid use, or relapse) **[BIII]**.

F. BMT candidates or recipients should be advised that certain activities and occupations (e.g., work in health-care settings, prisons, jails, or homeless shelters) may increase their risk of TB exposure. In deciding whether it is safe for a patient to continue activities in these settings, clinicians should consider the patient's specific duties, the precautions used to prevent TB exposure in the workplace, and the prevalence of TB in the community. The decision to continue or terminate such activities should be made jointly with the patient **[BIII]**. BMT recipients should avoid TB exposures, especially during the first 6 months post-BMT and during other periods of significant immunosuppression (e.g., GVHD, systemic steroid use, or relapse) **[BIII]**.

G. Immunocompromised BMT recipients and candidates undergoing conditioning therapy should avoid gardening or contact with soil and plants to reduce their exposure to potential pathogens such as *Toxoplasma gondii*, *Nocardia* spp., and *Aspergillus* spp., **[BIII]**. When this is unavoidable, BMT recipients, especially allogeneic BMT recipients, should wear gloves while gardening or touching plants or soil and should always wash their hands afterwards **[BIII]**.

H. Histoplasmosis following allogeneic BMT is rare. However, BMT recipients in histoplasmosis-endemic areas should avoid exposure to chicken coops and other bird-roosting sites and caves for the first 6 months post-BMT and during periods of significant immunosuppression (e.g., GVHD, systemic steroid use, or relapse) **[BIII]**.

II. Pet Safety

A. General prevention of zoonotic infections

1. Immunocompromised BMT recipients and candidates receiving conditioning therapy should minimize direct contact with animals (9) **[BIII]**. (See section *III.*) If BMT recipients choose to continue contact with pets, they should wash their hands after handling pets (especially if the handling occurs before eating) and avoid contact with pet feces to reduce the risk of toxoplasmosis, cryptosporidiosis, salmonellosis, and campylobacteriosis **[BIII]**. Adults should supervise handwashing in pediatric BMT recipients **[BIII]**.

2. Immunocompromised BMT recipients and candidates should not clean pet litter boxes or cages or dispose of animal waste **[DIII]**. If these cannot be avoided, patients should wear disposable gloves during such activities and wash their hands thoroughly afterwards **[BIII]**. Immunocompromised BMT recipients and candidates should avoid adopting pets < 6 months of age and any stray animals (2,3) **[DIII]**. Any pet that develops diarrhea should be checked by a veterinarian for infection with *Cryptosporidium* (2, 3), *Salmonella*, and *Campylobacter* (3) **[BIII]**.
3. Immunocompromised BMT recipients and candidates should not have contact with reptiles (e.g., snakes, lizards, turtles, iguanas, etc.) to reduce their risk of acquiring salmonellosis (10,11) **[DII]**. However, patients should be informed that salmonellosis may occur from fomite contact alone (12). Therefore, BMT recipients and candidates who have contact with a reptile, its food, or anything that it has touched should wash their hands thoroughly afterwards **[AIII]**.
4. Immunocompromised BMT recipients and candidates should avoid contact with ducklings and chicks because of the risk of acquiring *Salmonella* or *Campylobacter* spp. infections (10) **[BIII]**.
5. Immunocompromised BMT recipients and candidates should avoid contact with exotic pets (e.g., nonhuman primates) **[BIII]**.
6. Although bird droppings may be a source of *C. neoformans* or *H. capsulatum,* routine screening of healthy birds for *C. neoformans* or *H. capsulatum* is not recommended **[DIII]**.
7. BMT recipients should wear gloves while cleaning fish tanks to minimize potential exposure to *Mycobacterium marinum* **[BIII]**.

B. Prevention of toxoplasmosis

1. Most toxoplasmosis in the United States is acquired by eating undercooked meat. See section IV. Food Safety. However, all BMT recipients and candidates, especially those who are *Toxoplasma gondii* seronegative, should be informed of

the risks of contracting toxoplasmosis from cat feces **[BIII]**, but need not be advised to give away their cats **[DII]**. For households with cats, litter boxes should be cleaned daily by someone other than the BMT recipient during the first 6 months post-BMT and during periods of significant immunosuppression, (e.g., GVHD, steroid use, or relapse) to reduce the risk of transmitting toxoplasmosis to the BMT recipient **[BIII]**. Daily litter box changes will minimize the risk of fecal transmission of *T. gondii* oocysts, because fecal oocysts require at least 2 days of incubation to become infectious. If BMT recipients perform this task, they should wear disposable gloves during the first 6 months post-BMT and during periods of significant immunosuppression (e.g., GVHD, systemic steroid use, or relapse). Gloves should be discarded after a single use **[BIII]**. Soiled, dried litter should be disposed of carefully to prevent aerosolizing the *T. gondii* oocysts **[DIII]**. Cat feces (but not litter) may be flushed down the toilet **[BIII]**. Also, persons who clean cat litter, especially BMT recipients, should wash their hands thoroughly with soap and water afterwards to reduce their risk of acquiring toxoplasmosis **[BIII]**.

2. BMT recipients and candidates with cats should keep their cats inside **[BIII]** and should not adopt or handle stray cats **[DIII]**. Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats **[BIII]**. Pet cats of BMT recipients do not need to be tested for toxoplasmosis **[EII]**.
3. Playground sandboxes should be kept covered when not in use to prevent cats from soiling them **[BIII]**.
4. BMT recipients and candidates undergoing conditioning therapy should avoid drinking raw goat's milk to decrease the risk of acquiring toxoplasmosis **[BIII]**.

III. Water and Beverage Safety

A. Although little data are available regarding the risks for and epidemiology of Cryptosporidium disease in BMT recipients, it may be prudent for BMT recipients to avoid possible exposures to Cryptosporidium **[BIII]** since it has emerged as a

significant OI in other persons with severe immunosuppression (e.g., persons with HIV/AIDS).

B. BMT recipients should avoid walking, wading, swimming, or playing in recreational water that is likely to be contaminated with *Cryptosporidium, E. coli* 0157:H7 (10a, 10b), or sewage, or animal or human waste **[BII]**. BMT recipients should also avoid swallowing such water, (e.g., while swimming)(3, 10a) as well as any water taken directly from rivers and lakes (2,3) **[AIII]**.

C. If BMT recipients consume tap water, they should routinely monitor mass media (e.g., radio, television, newspapers) in their area in order to immediately implement any boil water advisories that may be issued for immunocompromised persons by state and local governments **[BIII]**. A boil water advisory means that all tap water, should be boiled for 1 minute before it is consumed.

D. Tap water not be completely free of Cryptosporidium. To eliminate the risk of Cryptosporidium exposure from tap water, BMT recipients may consider boiling tap water for 1 minute before consuming it (e.g., drinking, tooth-brushing) (3) **[CIII]**. Alternately, they may use certain types of water filters (2) or a home distiller (4) to reduce their risk of exposure to *Cryptosporidium* (3) and other water-borne pathogens **[CIII]**. If a home water filter* is used, it must be installed immediately before the water tap, and should be capable of removing particles <1 micrometer in size, or filter by reverse osmosis. BMT recipients should not use well water **[DIII]** because even annual coliform testing is too insensitive to detect sporadic water contamination. Bottled water may be consumed if it has been processed to remove Cryptosporidium by one of the 3 following processes: a) reverse osmosis, b) distillation, c) 1 micron absolute filtration. To confirm that a specific bottled water has undergone one of the above processes, BMT recipients may contact the bottler directly. To obtain the bottler's telephone number, contact the International Bottled Water Association at (703) 683-5213 from 9 a.m. to 5 p.m. EST.

C. Some patients may choose to take other precautions in the absence of boil-water advisories to further reduce their risk of cryptosporidiosis. These extra precautions

include avoiding fountain beverages and ice made from tap water at restaurants, bars, and theaters (3), fruit drinks made from frozen concentrate mixed with tap water, and iced tea or coffee made with tap water (4) **[DIII]**. Drinks that are likely to be *Cryptosporidium* spp. safe for BMT recipients to consume include nationally distributed brands of bottled or canned carbonated soft drinks and beers (3); commercially packaged noncarbonated drinks that contain fruit juice; fruit juices that do not require refrigeration until after opening, such as those that are stored unrefrigerated on grocery shelves (3); canned or bottled soda, seltzer or fruit drinks; steaming hot ($\geq$ 175^{o} F) tea or coffee (4); juices labeled as pasteurized; nationally distributed brands of frozen fruit juice concentrate that are reconstituted with water from a safe source (3).

D. BMT recipients should not drink unpasteurized milk, fruit or vegetable juices (e.g., apple cider, orange juice, etc.) to avoid infection with *Brucella* spp., *E. coli* 0157:H7, *Salmonella* spp., etc. (4a-e) **[DII]**.

IV. Food Safety

A. BMT candidates and household/family members preparing food for them post-BMT should be educated regarding food safety before the conditioning regimen (chemotherapy and radiation) begins **[BIII]**.

B. Food preparation and storage

1. Persons who prepare food for BMT recipients and candidates undergoing conditioning therapy should follow standard food shopping, storage, and preparation guidelines (14) **[AIII]**.
2. Raw poultry, meats, fish, and seafood should be handled on separate surfaces (cutting board, counter top) from other food items. Food preparers should always use separate cutting boards (one for poultry and other meats, one for vegetables and remaining cutting/carving tasks) **[AIII]**, and/or the board(s) should be washed with warm water and soap between cutting different food items **[AIII]**. To prevent food-borne illnesses such as *Campylobacter jejuni* and *Salmonella enteritidis*, which cause more severe and invasive infections in immuno-

compromised persons (15,16), uncooked meats should not come in contact with other foods **[BIII]**.

3. After preparing raw poultry, meats, fish, and seafood and before preparing other foods, food handlers should wash their hands and any cutting boards, counters, knives and other utensils used thoroughly in warm, soapy water **[AIII]**.
4. Allogeneic BMT recipients should wash their hands after contact with raw meat to prevent toxoplasmosis, salmonellosis, toxin producing *E. coli*, campylobacterosis, and yersiniosis **[AIII]**.
5. Persons preparing food for BMT recipients and candidates undergoing conditioning therapy should keep shelves, counter tops, refrigerators, freezers, utensils, sponges, towels, and other kitchen items clean **[AIII]**.
6. All fresh produce should be washed thoroughly under running water before serving (15a) **[AIII]**.

C. Persons preparing food for BMT recipients and candidates undergoing conditioning therapy should follow published USDA recommendations on safe food thawing (17) **[BIII]**.

D. Cooking guidelines

1. BMT recipients should not eat **any** raw or undercooked meat including beef, poultry, pork, lamb, venison or other wild game; and/or combination dishes containing raw or undercooked meats or sweetbreads from these animals such as sausages or casseroles **[AII]**. Also, BMT recipients should not consume raw or undercooked eggs or foods which may contain them (e.g., some preparations of hollandaise sauce, Caesar and other salad dressings, homemade mayonnaise, homemade eggnog, Orange Julius) because of the risk of infection with *Salmonella enteritidis* (16) **[AII]**. BMT recipients should not consume raw or undercooked seafood such as oysters or clams to prevent exposure to *Vibrios* spp. and viral gastroenteritis (16a-c) **[AII]**.
2. Persons preparing food for BMT recipients should follow established guidelines for monitoring internal cooking temperatures for meats (18) **[AII]**. For example, meat

should be cooked to an internal temperature of at least 150° F **[AII]**. The color of the meat after cooking does **not** reliably reflect the internal temperature. The only method for determining whether the meat has been adequately cooked is to measure its internal temperature with a thermometer. The following are recommended internal temperatures for different foods (per USDA):

- poultry 180° F
- solid red meats (beef, pork, lamb, veal, ham, chops) 160° F
- ground red meats and poultry 160° F
- casseroles and egg dishes (e.g., souffles) 160° F

Also, in situations where the BMT recipient or his or her caretaker does not have direct control over food preparation (e.g., when eating in restaurants), BMT recipients and candidates should only consume meat that is well-done **[AI]**. There is no evidence in the United States, to date, that eating food at a fast food restaurant is more risky than eating at a "conventional" sit-down restaurant.

4. Cold foods should be stored at < 40° F; hot foods should be kept at > 140° F **[BIII]**.
5. Persons preparing food for BMT recipients and candidates undergoing conditioning therapy should
   a. Wash their hands before and after handling leftovers **[AIII]**
   b. Use clean utensils and surfaces **[AIII]**
   c. Divide leftovers into small units and store in shallow containers for quick cooling **[AII]**.
   d. Refrigerate leftovers within 2 hours of cooking **[AII]**. Leftovers which are kept at room temperature for > 2 hours should be discarded **[AIII]**.
   e. Reheat leftovers or heat partially cooked foods to ≥165°F throughout before serving **[AII]**.
   f. Bring leftover soups, sauces, and gravies to a rolling boil before serving **[AIII]**.
   g. Follow published guidelines for cold storage of food (14) **[AII]**.

E. The diets of BMT recipients should be restricted to decrease the risk of exposure to food-borne infections from bacteria, yeasts, molds, viruses, and parasites **[BIII]**.

Currently, a low microbial diet is recommended for BMT recipients (19-21) **[BIII]**. This diet excludes raw fresh fruits and vegetables if they cannot be washed under running water before serving. In general, this diet should be continued for 3 months post-BMT for autologous BMT recipients. Allogeneic BMT recipients should remain on the diet until all immunosuppressive drugs such as cyclosporine, steroids, and tacrolimus, are discontinued. However, the transplant physician should have final responsibility for determining when the diet can be safely discontinued. Only one study has shown that dietary changes (such as consuming yogurt) have decreased the risk of mycotic infections (e.g., candidal vaginitis) (27). (A summary of high-risk foods and possibly safer food substitutions are included in Table 1).

F. In general, BMT candidates undergoing conditioning therapy and BMT recipients with neutropenia (ANC <1000/ml ^{3}), GVHD, immunosuppression, evidence of gastro-enteritis should avoid exposures to naturopathic medicines which may contain molds (28) **[DIII]**. BMT recipients wishing to take naturopathic medications are advised to use them only as prescribed by a licensed naturopathic physician working in consultation with the recipient's transplant and infectious disease physicians **[CIII]**.

V. Travel safety

Travel to developing countries may pose significant risks for exposure to opportunistic pathogens for BMT recipients, especially allogeneic recipients on chronic immuno-suppression.

A. BMT recipients should not plan travel to developing countries without consulting their physicians **[AIII]**. Travel should not occur until the period of severe immunosuppres-sion has resolved. In general, most allogeneic recipients should not plan travel to the developing world for 6-12 months post-BMT, especially if GVHD has occurred. Autologous transplant recipients may consider travel to the developing world 3-6 months after transplant if their physicians agree.

B. BMT recipients should be informed about strategies to minimize the risk of acquiring food- and water-borne infections while traveling. They should obtain updated, detailed health information for international travelers from health organizations (29, 30) **[AIII]**.

In general, while traveling in developing countries, BMT recipients should avoid consuming the following **[DIII]** :

- raw fruits and vegetables,
- tap water or any potentially untreated or contaminated water
- ice made from tap water or any potentially contaminated water
- unpasteurized milk or any unpasteurized dairy products
- fresh fruit juices.
- food and drinks from street vendors
- raw or undercooked eggs

Steaming-hot foods, fruits peeled by oneself, bottled and canned processed drinks, and hot coffee or tea are likely to be safe (31). Travelers should consider treatment of water when traveling. If bottled water is not available, then boiling is by far the best method to make water safe. However, if it is not feasible to boil water, then the traveler should carry supplies for disinfecting water such as commercially available iodine disinfection tablets, or a water filter (29).

C. Antimicrobial prophylaxis for traveler's diarrhea is not recommended routinely for BMT recipients traveling to developing countries **[DIII]** because traveler's diarrhea is not known to be more frequent or more severe in immunocompromised hosts. However, BMT providers who wish to provide prophylaxis to BMT recipients who are traveling may consider prescribing a fluoroquinolone such as ciprofloxacin or TMP-SMZ **[CIII]**, although resistance to TMP-SMZ is now common and resistance to quinolones is increasing in tropical areas. (See *Dosing Chart*.) Some experts recommend using bismuth subsalicylate to prevent traveler's diarrhea in adults (38). However, no data are available on safety and efficacy in BMT recipients, and salicylates are not recommended for use in persons < 18 years of age due to their association with Reye's syndrome (31).

D BMT recipient's immunization status should be assessed and immunizations updated as needed prior to travel. (See *Immunization* section).

Strategies for Safe Living References

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Footnote

* For a list of filters tested for *Cryptosporidium* removal, call the NSF International Consumer Line at 1-800-673-8010 or contact <http://www.nsf.org>.

Table 1. **High-risk foods and possibly safer food substitutions:**

High-risk foods to avoid:	**Possibly safer food substitutions:**
Raw and undercooked eggs (16) and foods containing them (french toast, omelettes, salad dressings, egg nog, puddings, etc.).	Pasteurized or hard boiled eggs.
Unpasteurized dairy products (milk, cheese, cream, butter, yogurt, etc.)	Pasteurized dairy products.
Fresh-squeezed, unpasteurized fruit and vegetable juices	Pasteurized juices.
Unpasteurized cheeses or cheeses containing molds	Pasteurized cheeses.
Undercooked or raw poultry, meats, fish, and seafood	Cooked poultry, well-done meats, cooked fish and seafood.
Vegetable sprouts such as alfalfa (32), bean, and other seed sprouts.	Avoid.
Raw fruits with a rough texture (e.g., raspberries).	Avoid.
Smooth raw fruits.	Wash under running water, peel or cook
Unwashed raw vegetables	Wash under running water, peel or cook
Undercooked or raw tofu	Cooked tofu. To cook, cut tofu into 1-inch cubes or smaller, and boil for at least 5 minutes in water or broth before eating or using in recipes.
Raw or unpasteurized honey	Avoid.
Deli meats, hot dogs, and processed meats.	Avoid unless cooked further.
Raw, uncooked grain products	Cooked grain products including bread, cooked and ready-to-eat cold cereal, pretzels, popcorn, potato chips, corn chips, tortilla chips, cooked pasta and rice.
Mate' tea (30)	Avoid
All moldy and outdated food products	Avoid
Unpasteurized beer (e.g., home-brewed and some micro brewery beer).	Pasteurized beer (most retail bottled, canned, and draft beer is pasteurized after fermentation).
Raw, uncooked brewers yeast	Avoid. BMT recipients should avoid contact with raw yeast, (e.g., should not make bread products themselves).
Unroasted raw nuts	Cooked nuts
Roasted nuts in the shell	Canned or bottled roasted nuts, nuts in baked products

TABLE 1. Proposed Schedule for Vaccination of Bone Marrow Transplant* (BMT) Recipients

* Includes all hematopoietic cell transplants from both blood and marrow

Vaccine	Post-BMT			Rating
	12 months	**14 months**	**24 months**	**Rating**
Inactivated Vaccines				
Diphtheria, tetanus, pertussis **< 7 years old** (a) **≥ 7 years old** (b)	DTAP or DT Td	DTaP or DT Td	DTaP or DT Td	**BIII** **BII**
Haemophilus influenzae type b conjugate (c)	Hib	Hib	Hib	**BII**
Hepatitis B (d)	Hep B	Hep B	Hep B	**BIII**
23-valent pneumococcal polysaccharide vaccine (e)	Pneumo		Pneumo	**BIII**
Hepatitis A (f)	Routine administration is not indicated.			**Not Rated** - limited data.
Influenza (g)	Lifelong, seasonal administration, beginning pre-BMT and resuming ≥ 6 months post-BMT is recommended.			**BII**
Meningococcal vaccine (h)	Routine administration is not indicated.			**Not Rated** - limited data.
Inactivated Polio Vaccine (I)	IPV	IPV	IPV	**BII**
Rabies (j)	Routine administration is not indicated.			**Not Rated** - limited data
Lyme disease	Routine administration is not indicated. No data on safety, efficacy, or immunigenicity of the lyme disease vaccine are available in BMT recipients.			**Not Rated** - limited data
Live Vaccines				
Measles-mumps-rubella (k,l, m)			MMR	**BIII**
Varicella (m, n, o)	Varicella vaccine use is contraindicated in BMT recipients. However, BMT candidates without impaired cell mediated immunity (19a) may receive varicella vaccination.			**EIII** **[CIII]**
Rotavirus	Contraindicated in BMT recipients, and in immunocompromised persons. No data on immunogenicity, safety, or efficacy in BMT recipients.			**EIII**

TABLE 1 FOOTNOTES

For the purposes of these guidelines, BMT recipients are presumed "immunocompetent" if they are ≥ 24 months post-BMT, are not on immunosuppressive therapy, and do not have graft-versus-host disease (GVHD).

a. Studies indicate that a BMT recipient may be primed if the donor has had primary series. Some studies indicate a recipient's antibody titer before BMT may affect the titer 1 year after BMT (1,2). No data are available on safety and immunogenicity of pertussis vaccination in BMT recipients.

b. BMT recipients should be revaccinated with Td every 10 years, as routinely recommended for all adolescents and adults (3,4).

c. *Haemophilus influenzae* type b (Hib)-conjugate vaccine is recommended for BMT recipients of any age (4,5).

d. Hepatitis B vaccination is recommended for persons ≤18 years of age and for adults who are undergoing dialysis or have behavioral risk factors for hepatitis B virus (HBV) infection. HBV-seronegative BMT candidates who are relatively immunocompetent and at increased risk of exposure to HBV should be immunized with hepatitis B vaccine. ACIP hepatitis B vaccination recommendations indicate that high doses (40 µg/dose) are recommended for adult dialysis patients and other immunocompromised adults (6,7,8). However, the optimal hepatitis B vaccination dose and schedule for BMT recipients has not been established.

e. The 23-valent pneumococcal polysaccharide vaccine polysaccharide pneumococcal vaccine may not be protective against pneumococcal infection in BMT recipients. The second dose of vaccine is not a booster dose, but provides a second chance for pneumococcal vaccination for persons who failed to respond to the first dose. Patients with chronic GVHD require adjunctive pneumococcal chemoprophylaxis (9).

f. No data are available on immunogenicity, safety, and efficacy of hepatitis A vaccine in BMT recipients. Some experts suggest that hepatitis A vaccination may be considered for investigational use in BMT recipients ≥24 months of age who are ≥12 months post-BMT **and** who have chronic liver disease, including hepatitis C infection or chronic GVHD **or** who are from areas experiencing outbreaks or have high hepatitis A incidence (10, 10a).

g. Children <9 years of age receiving influenza vaccination for the first time require two doses. Children ≤12 years of age should receive only split-virus influenza vaccine. Persons > 12 years of age may receive whole- or split-virus vaccine. ACIP/Red Book dosing schedule should be used (11,18). For optimal influenza prevention, both vaccination and influenza chemoprophylaxis should be used in BMT recipients.

h. Administration of meningococcal vaccine should be considered for BMT recipients who live in endemic areas or areas experiencing outbreaks (12). However, meningococcal vaccine immunogenicity and efficacy have not been studied in BMT recipients.

TABLE 1. FOOTNOTES (continued)

i. Inactivated polio virus (IPV) vaccine has been used successfully, although more data are needed on optimal methods and timing of immunization (13,14).

j. Clinicians may consider administering pre-exposure rabies vaccine to BMT recipients with potential occupational exposures to rabies (15). However, the safety and immunogenicity of rabies vaccination in BMT recipients has not been studied. Pre-exposure rabies vaccination should probably be delayed until at least 12 months, if not 24 months, post-BMT. Administration of rabies vaccine with human rabies immune globulin (HRIG) post-exposure may be administered any time post-BMT as indicated. Existing ACIP guidelines for post-exposure HRIG and vaccine administration should be followed, which include administering five doses of rabies vaccine given on days 0, 3, 7, 14, and 28 post-exposure (15,18).

k. The first dose of measles, mumps, rubella vaccine (MMR) should be given ≥24 months post-BMT if the BMT recipient is presumed immunocompetent. The second MMR dose should be given 6-12 months later; however, the benefit of a second dose in this population has not been evaluated. **[BIII]** During outbreaks, the second dose of MMR may be administered as early as 4 weeks after the first dose of MMR post-BMT (4).

l. The half life of intravenous immune globulin (IVIG or IGIV) is decreased in BMT recipients, but its effect on vaccine immunogenicity has not been evaluated. The ACIP/ Red Book-suggested intervals between administration of immune globulin preparations for various indications and vaccines containing live measles virus should be used (16,17,18).

m. Use of live vaccines such as MMR and varicella is indicated only in immunocompetent persons and are contraindicated for post-BMT recipients who are not presumed "immunocompetent" (17,19); see page 2, sentence 1 for definition of "immunocompetent."

n. When varicella vaccination is given to BMT candidates ≥13 years of age , two doses given 4-8 weeks apart are required. Further research is needed to determine safety, immunogenicity, and efficacy of varicella vaccine in BMT recipients (19).

o. Varicella vaccine is available to any physician free of charge from the manufacturer through a research protocol (20c) for use in patients who have acute lymphoblastic leukemia (ALL) who are a) are 12 months - 17 years of age, b) have disease that has been in remission for at least 12 continuous months, c) have a negative history of varicella disease, d) have a peripheral blood-lymphocyte count of >700 cells/mm^3, and e) have a platelet count of >100,000 cells/mm^3 within 24 hours of vaccination (19). The physician must provide information requested in the protocol, and the protocol and consent form for the study must be approved by the institution's Investigational Review Board. Information may be obtained about eligibility from the VARIVAX® Coordinating Center, Bio-Pharm Clinical Services, Inc., 4 Valley Square, Blue Bell, PA 19422; telephone (215) 283-0897 (19, 20d).

T**ABLE 1. FOOTNOTES (continued)**

Note 1: All indicated non-live vaccines should be administered to BMT recipients regardless of BMT type or presence of GVHD. Live, attenuated vaccines, such as MMR, varicella, rotavirus, *Bacillus Calmette-Guérin* (BCG), yellow fever, and oral typhoid vaccines, should **not** be given to any BMT recipient with active GVHD or immunosuppression (21). To date, there have been no reports of adverse events, such as exacerbation of GVHD, in immunized BMT recipients. However, data on immunization in BMT recipients are limited and further studies are needed to evaluate safety, efficacy, and immunogenicity of the proposed BMT immunization schedule.

Note 2: Use of combination vaccines is encouraged (21a). There are no contraindications to simultaneous administration of any vaccines (except cholera and yellow fever).

Note 3: Adverse events following vaccination should be reported promptly to the Vaccine Adverse Event Reporting System (VAERS), P.O. Box 1100, Rockville, MD 20849-1100. Forms and information may be obtained from VAERS by calling 1-800- 822-7967.

TABLE 2: Proposed Vaccinations for Family, Household Contacts, and Health Care Workers (HCWs) of BMT Recipients

Vaccine	Recommendations for Use	Rating
Hepatitis A	Routine hepatitis A vaccination is recommended during outbreaks, or for persons residing in endemic areas, especially for children in areas with high hepatitis A incidence (10, 10a).	**BII**
Influenza (a)	*Household contacts*: Influenza vaccination is strongly recommended during each influenza season beginning in the season before the transplant and continuing up to at least 24 months post-BMT. All household contacts of immune compromised BMT recipients should be vaccinated annually as long as these conditions persist (11). *HCWs and home care givers:* Annual influenza vaccination is strongly recommended during each influenza season (11, 20).	**AI** **AI**
Polio (b)	Vaccine is not routinely recommended for adults but should be administered when polio vaccination is indicated as per ACIP guidelines; when polio vaccine is administered, IPV is strongly preferred (13,20).	**AI**
Measles-mumps-rubella (c)	MMR vaccination is recommended for all persons who are ≥12 months old and who are not pregnant or immunocompromised (16, 17, 20).	**AI**
Rotavirus	In 1998, rotavirus vaccination was been routinely recommended for all immunocompetent infants at 2, 4, and 6 months of age (19b). Vaccination of infants who are close contacts of immunocompromised persons is acceptable because the benefits outweigh potential risks. However, preliminary post-vaccine licensure data has suggested that administration of rotavirus vaccine may be associated with intussusception (19c). Therefore, CDC recommending postponing administration of rotavirus vaccine to children scheduled to receive the vaccine before November, 1999, until further data are collected**.**	**AI before 7/99. DII curently**
Varicella (d)	Varicella vaccination is recommended for all susceptible persons who are ≥12 months old and who are not pregnant or immunocompromised. When varicella vaccination is given to persons ≥13 years of age, two doses are required, given 4-8 weeks apart (19, 20).	**AI**
Lyme disease (e)	Vaccination may be considered for persons ≥15 years of age residing, working, or recreating in areas of high or moderate risk areas (20a, 20b).	**CI**

T**ABLE 2. FOOTNOTES**

a. Chemoprophylaxis as adjunctive therapy may also be considered for HCWs or household contacts of BMT recipients. Children <9 years of age receiving influenza vaccination for the first time require two doses. Children ≤12 years of age should receive only split-virus influenza vaccine. Persons >12 years of age may receive whole- or split-virus vaccine (11,20).

b. **CAUTION: Vaccine strain polio virus in OPV can be transmitted person-to-person. Therefore, OPV administration is contraindicated in household contacts of immunocompromised persons.** If OPV is inadvertently administered to a household contact of an BMT recipient, ACIP/Red Book recommendations should be followed (13,18,20). Although vaccine-associated paralytic poliomyelitis (VAPP) has not been reported to date in BMT patients following exposure to household contacts inadvertently vaccinated with OPV, IPV should be used in household contacts and HCW to avoid person-to-person transmission of vaccine strain polio virus (13).

c. There is no evidence that live, attenuated vaccine strain viruses in MMR vaccine have ever been transmitted from person-to-person, other than rubella vaccine virus from a nursing mother to her infant (16).

d. If a HCW or a household contact of a BMT recipient develops a post-vaccination rash within 42 days of varicella vaccination, contact precautions should be implemented (19,20).

e. There are no data on safety and efficacy of lyme disease vaccine in children <15 years of age, or in immunocompromised persons.

TABLE 3: Proposed Vaccinations for BMT Recipients Traveling to Areas Endemic for other Vaccine-Preventable Diseases

Vaccine	Recommendations for Use	Rating
BCG (live vaccine)	The use of (live) BCG is contraindicated in BMT recipients < 24 months post-BMT and in all persons who are immunocompromised (21). Data on use in BMT recipients do not exist.	**EIII**
Cholera	Vaccination is not indicated. Data on safety and immunogenicity in BMT recipients do not exist (22).	**DIII**
Hepatitis A	No data are available on immunogenicity, safety, or efficacy of hepatitis A vaccine in BMT recipients. Therefore, immune globulin IM use is preferred for hepatitis A prophylaxis in BMT recipients. See Table 4 below. However, it does not replace avoidance behaviors, such as careful selection of food and water (10). Some experts suggest that hepatitis A vaccination may be considered for investigational use in BMT recipients ≥24 months of age who are ≥12 months post-BMT **and** who have chronic liver disease, including hepatitis C infection or chronic GVHD **or** who are from areas experiencing outbreaks or have high hepatitis A incidence (10, 10a). However, no recommendation can be made at this time due to limited data.	**Not rated - limited data.**
Japanese B encephalitis	No data are available on safety, immunogenicity, or efficacy in BMT recipients (23).	**Not rated - limited data.**
Lyme disease	No data are available on safety, immunogenicity, or efficacy in BMT recipients.	**Not rated - limited data.**
Meningococcal vaccine	Vaccine should be administered to BMT recipients traveling to endemic areas or to areas experiencing outbreaks (12). However, meningococcal vaccine immunogenicity and efficacy have not been studied in BMT recipients.	**Not rated** - limited data.
Plague	No data are available on safety, immunogenicity, or efficacy in BMT recipients (23a).	**Not rated - limited data.**
Polio (IPV only)	Booster dose may be given as indicated (13).	**CIII**
Rabies	Pre-exposure series should be administered to persons ≥12 months post-BMT if they anticipate travel to endemic areas (15).	**CIII**
Typhoid, oral (live vaccine)	The use of oral typhoid vaccine (live, attenuated strain) is contraindicated in BMT recipients <24 months post-BMT and in those who are immunocompromised (24). No data are available on safety, immunogenicity, or efficacy in BMT recipients.	**EIII**
Typhoid (IM)	No data are available on safety, immunogenicity, or efficacy in BMT recipients.	**Not Rated - limited data.**
Yellow Fever (live vaccine)	The use of (live) yellow fever vaccine is contraindicated in BMT recipients < 24 months post-BMT and in all immunocompromised persons (25). No data are available on safety, immunogenicity, or efficacy in BMT recipients.	**EIII**

NOTE: Specific advice for international travelers, including information on endemic diseases by country, is available through CDC's automated travelers' hotline at (404) 332-4559; by facsimile at (404) 335-4565; on the Internet at http://www.cdc.gov; and by file transfer protocol at ftp.cdc.gov.

TABLE 4: Proposed Use of Passive Immunization for BMT Recipients Exposed to Vaccine-Preventable Diseases

Preparation	Recommendations for Use	Rating
Cytomegalovirus immune globulin (CMVIG)	CMVIG is not recommended for CMV prophylaxis in BMT recipients because of its lack of efficacy (26).	**DI**
Hepatitis B immune globulin (HBIG)	HBIG is recommended as needed for hepatitis B exposure (6,7,8).	**CIII**
Human rabies immune globulin (HRIG)	HRIG should be administered with rabies vaccine at any time post-BMT as indicated for post-exposure rabies prophylaxis. Existing ACIP guidelines for post-exposure HRIG should be followed, with five doses of rabies vaccine give on days 0, 3, 7, 14, and 28 post-exposure (15,18).	**CIII**
Respiratory syncytial virus immune globulin (RSVIG) (a)	Given the high mortality from RSV pneumonia in BMT recipients, it would be reasonable for BMT centers to consider giving BMT recipients with RSV URI or LRI pre-emptive therapy with RSV-IVIG or high RSV titered IVIG to prevent severe disease and death from RSV pneumonia until controlled trials can be performed (27). (See *Viral Infections* section *II. RSV* and *Dosing Chart*.)	**CIII**
Tetanus immune globulin (TIG)	Post-exposure tetanus vaccine should be administered with or without TIG as indicated for tetanus exposure (3) at any time post-BMT.	**CIII**
Varicella zoster immune globulin (VZIG) (b)	VZIG should be administered to varicella-seronegative BMT recipients **within 96 hours of close contact with a person with varicella or shingles** if the BMT recipient is a) < 24 months post-BMT or b) ≥24 months post-BMT and still immunocompromised. VZIG administration may extend the varicella incubation period from 10-21 days to10-28 days. If the BMT recipient develops a varicella zoster virus (VZV)-like rash following contact or exposure to a person with varicella or herpes zoster, antiviral drug therapy should be administered until at least two days after all lesions have crusted (19).	**AII**
Intramuscular immune globulin (IMIG)	IMIG should be administered to BMT recipients who anticipate hepatitis A exposure, especially those <24 months post-BMT. It also should be administered following measles exposure in BMT recipients who were not vaccinated against measles post-BMT (16,28).	**BIII**
Intravenous immune globulin (IVIG or IGIV) (c)	IVIG may be considered for administration to BMT recipients with severe hypogammaglobulinemia (IgG <400 mg/dl) within the first 100 days post-BMT to prevent bacterial infections (29,30). (See *Bacterial Infections* section and *Dosing Chart*.)	**CIII**

TABLE 4 FOOTNOTES

a. Some experts recommend substituting RSVIG for IVIG for BMT recipients on replacement IVIG therapy during RSV season (18) **[CIII]**. However, no data are available demonstrating safety and efficacy of RSVIG use in BMT recipients.

b. If IVIG replacement therapy ($\geq$ 250 mg/kg) has been given < two weeks before varicella or zoster rash exposure, VZIG administration is probably not required. VZIG is distributed by the American Red Cross except in Massachusetts, where it is distributed by the Massachusetts Public Health Biologic Laboratories (now a unit of the University of Massachusetts) (19).

c. When given, serum IgG levels should be monitored regularly, (e.g., every two weeks).

NOTE: IVIG may be obtained from the American Red Cross Blood Services, although shortages occasionally occur. Physicians who have difficulty obtaining urgently needed IVIG and other immune globulin products are advised to contact any of the following: a) Alpha Therapeutic Corporation 1-800-421-0008; b) Bayer Corporation 1-800-288-8370; or c) Novartis Pharmaceuticals Corporation IVIG Hotline (973) 503-7500 or customer service 1-800-526-0175; or d) Immune Deficiency Foundation 1-800-296-4433. If IVIG still cannot be obtained after contacting the above listed organizations, physicians should contact the Food and Drug Administration (FDA) Product Shortage Officer, at the Center for Biologics Evaluation and Research (CBER) Office of Compliance (301) 827-6220.

TABLE 5: Vaccine Information

Vaccine Type	Trade Name	Licenced U.S. Manufacturers	Telephone	Recommended Storage Temperatures
DTaP	Tripedia®	Pasteur-Merieux-Connaught	1-800-VACCINE	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
	Infanrix®	SmithKline Beecham	1-800-877-1158	
	Acel-Imune®	Wyeth-Lederle	1-800-572-8221	
	Certiva®	North American Vaccine	1-888-628-2829	
DTP-Hib	Tetramune®	Wyeth-Lederle	1-800-VACCINE	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
	DTP/ACTHib®	Pasteur-Merieux-Connaught	1-800-366-8900	
DTaP-Hib	TriHibit®	Pasteur-Merieux-Connaught	1-800-VACCINE	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
Td Adult & DT-Pediatric	Generic	Pasteur-Merieux-Connaught	1-800-VACCINE	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
		Wyeth-Lederle	1-800-572-8221	
Hib	ACTHib®	Pasteur-Merieux-Connaught	1-800-VACCINE	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
	HibTITER®	Wyeth-Lederle	1-800-572-8221	
	PedvaxHIB®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	
	OmniHIB®	SmithKline Beecham	1-800-877-1158	
Hib-Hepatitis B	COMVAX®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
IPV	IPOL®	Pasteur-Merieux-Connaught	1-800-VACCINE	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
MMR	M-M-R II®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	Store at 2°- 8 °C (36°- 46°F). MMR vaccine may be frozen.
Measles/Rubella	M-R-Vax II®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	Store at 2°- 8 °C (36°- 46°F). M/R vaccine may be frozen.
Mumps/Rubella	Biavax II®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	Store at 2°- 8 °C(36°- 46°F). Mumps/Rubella vaccine may be frozen.
Measles	Attenuvax®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	Store at 2°- 8 °C (36°- 46°F). Measles vaccine may be frozen.
Mumps	Mumpsvax®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	Store at 2°- 8 °C (36°- 46°F). Mumps vaccine may be frozen.
Rubella	Meruvax II®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	Store at 2°- 8 °C (36°- 46°F). Rubella vaccine may be frozen.
Varicella	Varivax®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	Maintain continuously in a frozen state -15°C (5°F) or colder.
Hepatitis A	Vaqta®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
	Havrix®	SmithKline Beecham	1-800-877-1158	
Hepatitis B	Engerix-B®	SmithKline Beecham	1-800-877-1158	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
	Recombivax-B®	Merck Human Health Division	1-800-MerckRX (ordering) 1-800-NSCMerc (questions)	
Influenza	Fluzone®	Pasteur-Merieux-Connaught	1-800-VACCINE	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
	Fluvirin®	Evans Medical Ltd. *distributed by General Injectable and Vaccine (GIV)*	*1-800-521-7468*	
	Flu-Shield®	Wyeth-Lederle	1-800-572-8221	
	Fluogen®	Parkedale	1-888-358-6436	

TABLE 5: Vaccine Information (continued)

Vaccine Type	Trade Name	Licenced U.S. Manufacturers	Telephone	Recommended Storage Temperatures
Japanese encephalitis virus	JE-VAX	Research Foundation for Microbial Diseases of Osaka University, *distributed by Pasteur-Merieux-Connaught*	1-800-VACCINE	Store at 2°- 8°C (36°- 46°F). **Do not freeze**
Lyme disease	LYMErix™	SmithKline Beecham	1-800-877-1158	Store at 2°- 8°C (36°- 46°F). **Do not freeze**
Meningococcal	Menomune-A/C/Y/W-135®	Pasteur-Merieux-Connaught	1-800-VACCINE	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
Rabies	Generic	Michigan Biologic Products Institute *distributed by SmithKline Beecham*	(517) 335-8120 *1-800-877-1158*	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
	Imovax Rabies® & Imovax Rabies ID®	Pasteur-Merieux-Connaught	1-800-VACCINE	
	RabAvert™	Chiron Corporation	1-800-244-7668	
Rotavirus	Rotashield™	Wyeth-Lederle	1-800-572-8221	Can be stored at room temperature, or Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
Typhoid	Typhoid Vaccine, U.S.P.	Wyeth-Lederle	1-800-572-8221	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.
Typhoid, Vi polysaccharide	Typhim Vi	Pasteur-Merieux-Connaught	1-800-VACCINE	Store at 2°- 8°C (36°- 46°F). **Do not freeze**.

Note 1: Persons requesting additional information on vaccines should contact the CDC Immunization Hotline at 1-800-CDC-SHOT (1-800-232-7468) or access CDC's National Immunization Program Internet Home Page at http:// www.cdc.gov/nip.

Note 2: Adverse events following vaccination should be reported promptly to the Vaccine Adverse Event Reporting System (VAERS), P.O. Box 1100, Rockville, MD 20849-1100. Forms and information may be obtained from VAERS by calling 1-800- 822-7967.

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Note: ACIP Immunization Guidelines can be accessed from CDC's National Immunization Program Internet Home Page at http://www.cdc.gov/nip or contact the CDC Immunization Hotline at 1-800-CDC-SHOT.

BLOOD AND MARROW SAFETY

Note: Allogeneic BMT is a unique situation in which the life of the BMT recipient may depend on the timely selection of an acceptably HLA-matched donor. Few, one, or no potentially HLA-matched donors may be identified. Hence the transplant physician may have to, and often does, tolerate a slightly greater risk of transmission of an infectious agent through BMT than would be permitted for routine blood transfusion. If the only possible donor is at risk for or known to be infected with a blood-borne pathogen, and the patient is likely to succumb rapidly from his or her disease if not transplanted, the BMT physician must carefully weigh the risks and benefits of using infected or potentially infected donor cells. No person should be denied a potentially life-saving BMT procedure based solely on an infectious disease deferral cited below. Whether to select a donor (including an unrelated UCB donor) who is at risk for or has an infectious disease transmissible by BMT, should be determined on a case-by-case basis **[AIII];** and is the final responsibility of the BMT physician **[AIII].** This section provides guidance for the BMT physician by detailing strategies to minimize transmission of infectious diseases, whenever possible, from donors to recipients.

I. Prevention of transmission of infections from BMT donors to recipients

A. All BMT donor-collection sites should follow published guidelines and standards for donor screening (e.g., medical history, physical exam, and serologic testing) within 30 days before donation to detect potentially transmissible infections (1-6) **[BII]**.

B. All prospective BMT donors should be evaluated by a history and physical examination to determine their general state of health and whether they pose a risk of transmitting infectious diseases to the BMT recipient (3). All BMT donors should be in good general health (3)**[BIII]**. Acute or chronic illness in the prospective BMT donor should be investigated to determine the etiology. In general, ill persons should not be BMT donors **[DIII]**.

1. A flu-like illness in a prospective donor at the time of evaluation should prompt consideration of and serologic testing for infections that might pose a risk to the

recipient, (e.g., Epstein-Barr virus [EBV], cytomegalovirus [CMV], *Toxoplasma gondii*)**[BIII]**. Persons with a positive serum EBV-VCA IgM but negative serum EBV-VCA IgG should not serve as donors for allogeneic T-cell depleted BMT, especially for unrelated/mismatched transplants, until their serum EBV-VCA IgG becomes positive **[DIII]**. Persons with acute toxoplasmosis should not donate until the acute illness has resolved **[DII]**.

2. Prospective donors with symptoms suggestive of active tuberculosis (TB) (6) should be screened for active TB (6) **[BIII]**. Prospective donors with active TB should not donate until the TB is well-controlled following appropriate medical therapy **[EIII]**. However, there is no known risk from transplanting marrow from an untreated, tuberculin-positive donor who has no evidence of active disease. It is not necessary to screen potential donors for TB with Mantoux skin tests **[DIII]**. (See *Hospital Infection Control* section *XI.*)
3. Prospective BMT donors who reside in or have traveled to areas endemic for rickettsia and/or tick-borne pathogens and have evidence of an acute tick-borne infection should be temporarily deferred as donors until infection with these pathogens are excluded **[DIII]**. Relevant pathogens include *Rickettsia rickettsii, Babesia microti*, *Coxiella burnetii*, and the Colorado Tick Fever virus, which are the etiologic agents of Rocky Mountain spotted fever, babesiosis, Q fever, and Colorado Tick Fever, respectively; these pathogens have been documented to be transmitted by blood transfusion (11-15). In addition, some experts have recommended deferring persons with active human granulocytic ehrlichiosis (HGE) from BMT donation (16) **[CIII]**.

C. The medical history of the prospective BMT donor (or donor's mother in the case of a UCB donor) should include:
   1. A history of documented immunizations (1) in the last six months, and any history of ever being vaccinated for hepatitis B **[AII]**. BMT donation should be deferred for 4 weeks after the donor receives any live-attenuated vaccine (e.g., rubeola [measles], mumps, rubella [German measles], oral polio, varicella [chicken pox], yellow fever,

and oral typhoid vaccines)**[EIII]**. This deferral will avoid the possibility of infusing a live infectious agent into a BMT recipient. BMT donation need not be deferred in persons who have recently received toxoid, or killed viral, bacterial, or rickettsial vaccines as long as the donor is asymptomatic and afebrile (7) **[BIII]**. Donations can also be accepted from donors who have recently received any of the following killed, inactivated, or recombinant vaccines: tetanus, diphtheria, hepatitis A, hepatitis B, cholera, influenza, meningococcal, paratyphoid, pertussis, plague, polio (inactivated polio vaccine [IPV]), rabies, typhoid (inactivated I.M. vaccine), or typhus vaccines (7).

2. A travel history **[BIII]** to determine whether the donor has ever resided in or traveled to countries with endemic diseases which may be transmitted through BMT such as malaria. Permanent residents of non-endemic countries who have traveled to an area considered endemic for malaria by CDC may be accepted as BMT donors if 1 year has elapsed since their departure from the endemic area and they have been free of malaria symptoms, regardless of whether they received antimalarial chemo-prophylaxis. Persons who have had malaria and received appropriate treatment should be deferred from BMT donation for 3 years after becoming asymptomatic. Immigrants, refugees, citizens, or residents (for at least 5 years) of endemic countries may be accepted as BMT donors if 3 years have elapsed since departure from the malarious area and they have been free of malaria symptoms.
3. History of Chagas disease, leishmaniasis, babesiosis. Persons with these diseases should not serve as BMT donors **[DIII]**. Some experts also recommend deferral for a past history of these illnesses (7) [CIII].
4. A history of any deferral from plasma or blood donation. The reason for such a deferral (3) and whether it was based on an infectious disease should be investigated **[BIII]**.
5. History of viral hepatitis. Persons with this history should be investigated to determine if they are still infectious and if so, they should be excluded from donation **[DIII]**.

7. A history of blood product transfusion, solid organ transplantation, or transplantation of tissue containing viable leukocytes within the last 12 months (3) **[BIII]**. Such persons should be excluded from BMT donation **[DIII]**. Persons who have received xenografts should be indefinitely excluded from donation **[EIII]**.
8. A history of risk factors for Creutzfeldt-Jakob Disease (CJD, including a blood relative with CJD, receipt of a human pituitary-derived hormones such as growth hormones or gonadotrophins, or receipt of a dura mater graft (6, 6a, 8) **[BIII]**. Although the clinical latency period for iatrogenic CJD may be > 30 years (8), transmission of CJD by blood products is highly unlikely (8), and no CJD has ever been reported in BMT recipients, persons with a history of the CJD risk factors listed above should be excluded from donation for unrelated BMT **[DIII]** if a choice exists between two otherwise equally suitable donors. Some experts also recommend assessing potential donors for risk factors for bovine spongiform encephalopathy (BSE) or new variant Creutzfeldt-Jakob Disease (nvCJD), including a history of cumulative travel or residence in the United Kingdom for 6 months or more between 1980 and 1996 or receipt of bovine insulin or other injectable products made from cattle from countries with BSE (8) **[CIII]**.
9. Past medical history which suggests that the donor has clinical evidence of (4) or is at high risk for acquiring a blood-borne infection (e.g., HIV-1/2, HTLV-I, HTLV-II, HCV, or HBV) (6), including
    a. men who have had sex with another man in the preceding 5 years (4, 6)**[BIII]**;
    b. persons who report nonmedical intravenous, intramuscular, or subcutaneous injection of drugs in the preceding 5 years (4)**[BIII]**;
    c. persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates (4)**[BIII]**;
    d. men and women who have engaged in sex in exchange for money or drugs in the preceding 5 years (4)**[BIII]**;
    e. persons who have had sex in the preceding 12 months with any person described above (4), or with a person known or suspected to have HIV (4) or hepatitis B

infections **[BIII]**;

f. persons who have been exposed in the preceding 12 months to known or suspected HIV, HBV, and/or HCV-infected blood through percutaneous inoculation or through contact with an open wound, nonintact skin, or mucous membrane (4)**[BIII]**;

g. inmates of correctional systems (4) and individuals who have been incarcerated for more than 72 consecutive hours during the previous 12 months **[BIII]**;

h. persons who have had or have been treated for syphilis or gonorrhea during the preceding 12 months (3)**[BIII]**;

i. persons who within 12 months have undergone tattooing, acupuncture, ear or body piercing (9) in which shared instruments are known to have been used **[BIII]**.

Persons reporting any of the past medical history listed above should be excluded from donation **[DIII]**.

D. The following serologic tests should be performed for each prospective donor: HIV-1 Ag, anti-HIV-1/2, anti-HTLV-I/II, HBsAg, total anti-HBc (both IgG and IgM), anti-HCV, anti-CMV, and a serologic test for syphilis (3, 6)**[AIII]**. FDA-licensed or approved donor-screening tests should be used and only by laboratories appropriately certified for these tests **[AIII]**. Potential donors who refuse infectious disease testing, especially for HIV-1/2, should be excluded as BMT donors (4)**[EIII]**. In general, those who have repeatedly reactive screening tests for anti-HIV-1/2, anti-HTLV-I/II, anti-HCV, HBsAg, or anti-HBc should be excluded as BMT donors (4) **[EII]**. All infectious disease testing and results should be reported to the transplant physician before the BMT candidate's conditioning regimen begins (4) **[AIII]**.

E. If two equally well-matched potential allogeneic BMT donors are identified and one is seropositive for CMV, the person who is CMV seronegative should be selected preferentially as the donor **[BIII]** for CMV seronegative BMT recipients. However, there are no data indicating that such donor selection is beneficial for CMV seropositive BMT recipients.

F. All BMT centers should keep records of BMT harvesting, processing, testing, cryo-preservation, storage, and infusion or disposal of each aliquot of donated hematopoietic progenitor cells for at least 10 years after the date of implantation, transplantation, infusion or transfer of the product (2)**[AIII]**. If that date is not known, however, then records should be retained at least 10 years after the product's distribution, disposition, or expiration, whichever is latest.

II. Umbilical cord/placental blood donation

A. Within 48 hours of umbilical cord blood (UCB) collection, women delivering potential UCB donor infants should be screened by interview for the presence of blood-borne infections that might pose a risk for the BMT recipient if transmitted by BMT as listed in section I for all prospective BMT donors (6) **[AIII]**. In addition, a sample of the mother's blood should be collected within 48 hours of the child's birth and UCB collection **[BIII]** and should be tested for the presence of those blood-borne infections within 7 days of UCB collection **[BIII]**. UCB units from infants whose mothers report risk factors for **[DIII]**, or are repeatedly reactive in screening tests for blood-borne infections **[EIII]** should not be used for transplantation.

B. UCB donations should be collected using sterile technique (18) **AIII]**.

C. Donated UCB may be tested for the presence of anti-HIV-1/2, anti-HTLV-I/II, HBsAg, anti-HBc, anti-HCV, syphilis, and for anti-CMV IgM (19)**[CIII]**, although providers should be aware that CMV IgM tests of placental blood may be negative in 20%-40% of congenital CMV infections (18). In general, UCB donations that test positive or are repeatedly reactive on screening tests for any of these agents should not be used for BMT donation **[DIII]**. (See section V.)

III. Pediatric donors related to the potential BMT recipient

A. Children > 18 months of age who are born to mothers with or at risk for HIV infection, who have not been breast fed within the last 12 months, and whose HIV antibody tests, physical examination and medical records do not indicate evidence of HIV infection

can be accepted as donors (4)**[BIII]**.

B. Children ≤ 18 months of age who are born to mothers with or at risk for HIV infection and who have not been breast fed from an HIV-infected woman within the past 12 months may be accepted as donors ONLY IF HIV infection has been excluded according to established criteria (20)**[BIII]**. Children who have been breast fed from an HIV-infected woman within the past 12 months should be excluded as stem cell donors regardless of HIV infection status **[AIII]**.

C. The mother and, if possible, the father of all pediatric stem-cell donors who are at risk for perinatal transmission of HIV and other blood-borne infections, should be interviewed by a health-care professional competent to elicit information regarding risk factors for possible blood-borne infection in the potential pediatric donor **[AIII]**.

D. Children who meet any of the adult donor exclusion criteria should not become BMT donors (4)**[EIII]**. (See **I**.)

IV. Prevention of infection from extraneous contamination of donated units

A. BMT centers should follow current standards to detect and prevent extrinsic bacterial a and fungal contamination of collected stem cell units at the collection site and at the transplant center, before the units are transplanted (3)**[AIII]**.

B. Until further data are available regarding risk of infection from UCB donations, fungal and aerobic bacterial cultures should be performed on each UCB donation by the collection center during initial processing and freezing **[BIII]**. Some experts also recommend anaerobic bacterial cultures **[CIII]**. If bacterial culture results are positive, antibiotic-susceptibility tests should be performed. Results of cultures and antibiotic-susceptibility tests should be provided to the transplant center prior to the transportation of the UCB donation. Some experts recommend that bacteriologic and fungal culture be performed again at the transplant center after the UCB donation is thawed and before the BMT is performed **[CIII]**.

V. Using potentially infectious hematopoietic stem/progenitor cells

Whenever possible, BMT physicians should avoid transplanting any infected or infectious donor hematopoietic progenitor cell product unless the risk of death of not using these cells for transplantation is deemed to be greater than the risk of death from the infectious disease **[AII]**. If such a product is selected for use, the following should be documented in the BMT recipient's chart: a) knowledge and authorization of the recipient's BMT physician regarding the potential for transmission of an infectious agent during BMT, and b) written advance informed consent from the recipient or recipient's legal guardian acknowledging the possible transmission of an infectious agent during the transplant **[AIII]**. Subsequently, the BMT physician should include the infectious agent in the differential diagnosis of any illness that the BMT recipient develops, so that the infection, if transmitted, can be diagnosed early and treated pre-emptively, if possible. Such infectious products (with the exception of those in which CMV seropositivity is the only evidence of infectiousness) should be labeled as "BIOHAZARD" or "untested for BIOHAZARDS" as applicable. Tissue intended for autologous use should be labeled "FOR AUTOLOGOUS USE ONLY."

VI. Pediatric Notes

No national standards exist for fetal/*in utero* BMT, and the overall risks of transmitting infections to a fetus through this investigational procedure (21, 22) has not been determined. However, in addition to precautions appropriate for adult recipients, clinicians performing *in utero* BMT are advised to evaluate potential donors for evidence of active infectious diseases which could cause serious congenital infections in the transplanted fetus (e.g., rubella, varicella, CMV, syphilis, or *T. gondii*)**[CIII]**.

Blood and Marrow Safety References

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DRUG DOSING CHART

Drug Regimens for Prophylaxis of opportunistic infections in Adult and Adolescent BMT recipients

Preventive regimens

Pathogen	Indication	First choice	Alternatives
CMV	Universal prophylaxis of CMV disease to all "at risk" allogeneic BMT recipients throughout Phase II, (e.g., from engraftment to day +100 post-BMT). OR Pre-emptive CMV treatment given <100 days post-BMT to all "at risk" allogeneic BMT recipients. Start GCV when the patient develops any level of CMV antigenemia or viremia. (See *Viral Infections* section for definition of "at risk" allogeneic BMT recipients.)	Ganciclovir (GCV) 5-10 mg/kg/d ÷ q 12 h i.v. x 10-14 days, followed by 5-6 mg/kg/dose q.d. i.v. for 5 days/week from engraftment until day +100 post-BMT **[AI]**. GCV 5 mg/kg i.v. q 12 h x 7 days, followed by 5 mg/kg/d given 5 days/week until day + 100 post-BMT or for a minimum of 3 weeks, whichever is longer **[AI],** OR give GCV for a total of 3 - 6 weeks. Be prepared to reinstitute GCV if subsequent weekly CMV antigenemia screening tests become positive **[CII]**.	Foscarnet 180 mg/kg/day i.v. ÷ q 12 h x 7 days followed by 90-120 mg/kg/day until day 100 **[CIII].** Note: Patients who do not tolerate standard doses of GCV should be given Foscarnet.
	Pre-emptive treatment for CMV sero-positive autologous BMT recipients < 100 days post-BMT. Start GCV when antigenemia is ≥ 5 cells/slide	GCV 5 mg/kg/dose i.v. q 12 h x 7 days followed by 5 mg/kg/day i.v. on 5 days/week x 2 weeks **[BII]**.	
	Pre-emptive treatment of allogeneic BMT recipients > day 100 post-BMT. Start GCV when: 1. antigenemia is ≥ 5 cells/slide or 2. the patient has had at least one consecutively positive viremia or PCR tests, (e.g., such as in a person receiving steroids for GVHD, or who received GCV at <100 days post-BMT).	GCV 5 mg/kg/dose i.v. q 12 h x 7 days followed by 5 mg/kg/day i.v. on 5 days/week x 2 weeks **[BIII]**.	

HSV	Prevention of HSV reactivation in HSV seropositive BMT recipients. Start Acyclovir at the beginning of conditioning therapy and continue until engraftment or until mucositis resolves (approximately 30 days post-BMT in allogeneic BMT recipients).	Acyclovir 200 mg p.o. t.i.d. or 400 mg p.o. b.i.d. or 250 mg/m^2/dose infused over 1 hr i.v. q 12 h **[BIII]**.	For adults > 35 kg, Valacyclovir 500 mg p.o. bid **[CIII]** OR For adults < 35 kg, Valacyclovir 250 mg p.o. b.i.d. **[CIII]** or Acyclovir susp. 4 mg/kg p.o. b.i.d. **[BIII]** Note: For patients requiring prophylaxis for both CMV and HSV post-BMT, Ganciclovir alone provides effective prophylaxis for both CMV and HSV.
VZV	Prevention of VZV disease following VZV exposure in VZV seronegative BMT recipients who are < 24 months post-BMT, or are ≥24 months post-BMT and on immunosuppressive therapy or have chronic GVHD. Give within 96 h (preferably 48 h) after close contact with a person with either chickenpox or shingles.	Varicella zoster immune globulin (VZIG), 5 vials (1.25 ml each or 625 mg total) i.m. x **1 [AII]**.	None
Influenza	Prevention of influenza A and B in BMT recipients. (See *Immunization* section.) Prophylaxis and pre-emptive treatment in BMT recipients during community and nosocomial outbreaks of influenza A.	Lifelong annual seasonal influenza vaccination starting before BMT and restarting 6 months after BMT **[BIII]**. Whole or split virus influenza vaccine 0.5 ml i.m./dose Rimantadine 100 mg p.o. b.i.d. **[CIII]**	 Amantadine 100 mg p.o. b.i.d. **[CIII]**

Bacterial infections	Prevention of bacterial infections in allogeneic BMT recipients with severe hypogammaglobulinemia (serum IgG level < 400 mg/dl) within the first 100 days post-BMT.	Intravenous immune globulin (IVIG) 125 mg/kg/week (500 mg/kg/month). If serum IgG levels remain < 400 mg/dl, may raise dose to 250 mg/kg/week **[CIII]**.	None NOTE: 1. IVIG is contraindicated in patients with anti-IgA antibodies **[DIII]**. 2. Some experts recommend checking serum IgG levels q 2 weeks in patients receiving IVIG replacement therapy. 3. See *Bacterial Infection*s section footnote for information on how to obtain IVIG.
Streptococcus pneumoniae	Prevention of pneumococcal disease in BMT recipients.	23-valent pneumococcal polysaccharide vaccine at 12 and 24 months post-BMT **[BIII]**.	Note: 1. Penicillin resistant *S. pneumoniae* is increasing in the United States. 2. See *Immunization* section.
Haemophilus influenzae type type b	Prevention of invasive *Haemophilus influenzae* type b (Hib) disease in BMT recipients. Prophylaxis of invasive Hib disease in BMT recipients who are exposed to persons with *H. influenzae* type b disease (1).	*Haemophilus influenzae* type b conjugate vaccine for all BMT recipients at 12, 14, and 24 months post-BMT **[BII]**. (See *Immunization* section.) Rifampin 600 mg p.o. q.d. x 4 days **[BIII]**.	None
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Elimination of MRSA carrier state to prevent MRSA disease in chronic carriers.	Mupirocin calcium ointment 2%. Using a cotton-tip applicator or equivalent, apply to nares bid x 5 days, or to wounds qd x 2 weeks.	None.
Candida spp.	Prophylaxis for disease from fluconazole-susceptible *Candida* spp. in allogeneic BMT recipients. Give from the day of transplantation (day 0) until engraftment (approximately 30 days post-BMT), or until 7 days after the ANC > 1,000 cells/mm^3.	Fluconazole, 400 mg. p.o. or i.v. q.d. **[AI]**.	None

Pneumocystis carinii	Prophylaxis of *Pneumocystis carinii* pneumonia (PCP) in: 1. all allogeneic, BMT recipients, and 2. autologous BMT recipients with underlying hematologic malignancies such as lymphoma or leukemia, for those receiving intense conditioning regimens or graft manipulation, or for those who have recently received fludarabine or 2-chlorodeoxyadeno-sine (2-CDA) (3). Give PCP prophylaxis from the time from engraftment for at least 6 months post-BMT. Continue beyond 6 months post-BMT for the *duration of immunosuppression for all persons who* 1) are receiving immuno-suppressive therapy (e.g. prednisone or cyclosporine) or who 2) have chronic GVHD.	Trimethoprim-Sulfamethoxazole (TMP-SMZ) **[AII]**, Dose: 1 DS p.o. q.d. OR 1 SS p.o. q.d. OR TMP-SMZ 1 DS p.o. t.i.w. Some experts recommend giving PCP prophylaxis for 1-2 weeks prior to BMT (day -14 to day -2) **[CIII]**.	Dapsone **[BIII]** 50 mg p.o. b.i.d. or 100 mg p.o. q.d. OR Pentamidine 300 mg q 3-4 weeks via Respirgard II ™ nebulizer **[CIII]**. Note: Patients who are receiving sulfadiazine-pyramethamine for toxo-plasmosis therapy are protected against PCP and do not need additional PCP prophylaxis. (See *T. gondii* section.)
Toxoplasma gondii	Prophylaxis of *T. gondii* disease in *T. gondii* seropositive allogeneic BMT recipients. Start after engraftment and give as long as patients remain on immunosuppressive therapy (generally until 6 months post-BMT).	Trimethoprim-Sulfamethoxazole (TMP-SMZ) **[AII]**, Dose: 1 DS p.o. q.d. OR 1 SS p.o. q.d. OR TMP-SMZ 1 DS p.o. t.i.w.	For those who are intolerant to TMP-SMZ, the following drugs can be substituted: Clindamycin 300-450 mg p.o. q 6-8 h AND pyrimethamine 25-75 mg p.o. q.d. *plus* leucovirin 10-25 mg p.o. q.d. - q.i.d. **[CIII]** Note: In allogeneic BMT recipients, clinical toxoplasmosis has occurred despite the use of TMP-SMZ for PCP prophylaxis (5).

Strongyloides spp.	Prevention of strongyloidiasis hyperinfection in BMT candidates whose pre-BMT screening tests are positive for *Strongyloides* spp., or who have an unexplained eosinophilia and a compelling travel or residence history suggestive of exposure to *S. stercoralis.* Should be given before BMT.	Ivermectin 200 μg/kg p.o. q.d. x 2 consecutive days (6,7) **[BIII]**. 1 tablet = 6 mg. Body Weight (kg) — Oral Dose < 15 kg — Not recommended ≥ 15 - 24 — ½ tablet 25-35 — 1 tablet 36-50 — 1½ tablets 51-65 — 2 tablets 66-79 — 2½ tablets ≥80 — 200 μg/kg (Note: In the immunocompromised, multiple courses at two week intervals may be required. However, cure may not be achievable. Safety and efficacy of Ivermectin has not been established during pregnancy.)	1) Albendazole 400 mg p.o. q.d. X 3 d OR 2) Thiabendazole 25 mg/kg p.o. b.i.d. x 2 days **[BIII]**. Maximum dose = 3 g/24h. NOTE: Albendazole and Thiabendazole are contraindicated in pregnancy.

Traveler's diarrhea	Prophylaxis in BMT recipients who are immunocompromised and are traveling in developing countries.	Ciprofloxacin 500 mg. p.o. q.d. for the duration of stay in developing countries **[BIII]**. or Bismuth subsalicylate 2 ounces po qid ot 2 tablets po qid. May use for up to 3 weeks to prevent travelers' diarrhea in adults > 18 years of age only. WARNING: **Use of aspirin-containing products including Bismuth sub-salicylate is contraindicated in persons < 18 years of age** unless prescribed by a physician because they have been associated with Reye syndrome (11).	TMP-SMZ, one DS tablet p.o. q.d. for the duration of stay in developing countries **[CIII]**. Note: Ciprofloxacin, Norfloxacin, and Ofloxacin are not approved for use in children < 18 years of age.

Mycobacteria tuberculosis (TB)	Prevention of TB in: 1. highly immunocompromised BMT recipients or candidates who have been significantly exposed to someone with active, infectious (e.g., sputum smear positive) pulmonary or laryngeal tuberculosis, regardless of the BMT recipient's or candidate's TST status, and 2. BMT recipients or candidates with a positive TST and who were not previously treated and have no evidence of active TB disease.	Isoniazid 300 mg/day p.o. or i.m. x 9 months (for at least 270 doses) (8), AND Pyridoxine (Vitamin B_6) 25-50 mg p.o. q.d. Give to nutritionally deficient BMT recipients and candidates while on INH-PT, to reduce the occurrence of INH-induced neuropathy (8) **[BIII]**.	1. A twice weekly (b.i.w.) schedule of INH and Pyridoxine may be considered before BMT **[CIII]**. The biweekly INH dose is 900 mg p.o. or i.m. b.i.w. The biweekly Pyridoxine dose is 50-100 mg p.o. b.i.w. 2. A 2 month pyrazinamide/rifampin (PZA/RIF) preventive therapy (PT) regimen may be considered before BMT in those who are not at risk for serious rifampin drug interactions and whose BMT is not scheduled until at least 2 weeks after the 2 month course of PZA/RIF is completed (8,9) **[CIII]**. PZA dose is 20-40 mg/kg/day p.o. or 50 mg/kg per dose p.o. b.i.w. Maximum daily PZA dose = 2 g. RIF dose is 10-20 mg/kg/day p.o. or i.v. or 10-20 mg/kg per dose given b.i.w. p.o. or i.v. Maximum daily RIF dose is 600 mg. 3. Routine use of a two month PZA/RIF PT regimen is not recom-ended after BMT due to the risk of serious rifampin drug interactions **[DIII]**. 4. Persons who have been exposed to a rifamycin and isoniazid drug-resistant TB should be placed on PT regimens that involve at least two anti-TB drugs to which the infecting strain is susceptible (8) **[BIII]**, 5. For patients who are intolerant to INH, a TB expert should be consulted **[AIII]**.

Prophylaxis for opportunistic infections in pediatric BMT recipients

Pathogen	Indication	Preventive regimens: First choice	Preventive regimens: Alternatives
CMV	Universal prophylaxis of CMV disease to all "at risk" allogeneic BMT recipients throughout Phase II, (e.g., from engraftment to day +100 post-BMT). OR Pre-emptive CMV treatment given <100 days post-BMT to all "at risk" allogeneic BMT recipients. Start GCV when the patient develops any level of CMV antigenemia or viremia. (See *Viral Infections* section for definition of "at risk" allogeneic BMT recipients.)	Ganciclovir (GCV) 5-10 mg/kg/d ÷ q 12 h i.v. x 10-14 days, followed by 5-6 mg/kg/dose q.d. i.v. for 5 days/week from engraftment until day +100 post-BMT **[AI]**. GCV 5 mg/kg/dose i.v. q 12 h x 7 days, followed by 5 mg/kg/d given 5 days/week until day +100 post-BMT or for a minimum of 3 weeks, whichever is longer **[AI]**, OR give GCV for a total of 3 - 6 weeks. Be prepared to reinstitute GCV if subsequent weekly CMV antigenemia screening tests become positive **[CII]**.	Foscarnet 180 mg/kg/day i.v. ÷ q 12 h x 7 days followed by 90-120 mg/kg/day until day 100. **[CIII]**. Note: Patients who do not tolerate standard doses of GCV should be given Foscarnet.
	Pre-emptive treatment for CMV sero-positive autologous BMT recipients <100 days post-BMT. Start GCV when antigenemia is ≥5 cells/slide.	GCV 5 mg/kg/dose i.v. q 12 h x 7 days followed by 5 mg/kg/day i.v. on 5 days/ week x 2 weeks **[BII]**.	
	Pre-emptive treatment of allogeneic BMT recipients >100 days post-BMT. Start GCV when: 1. antigenemia is ≥5 cells/slide or 2. the patient has had at least 1 positive PCR or viremia test, (e.g., such as in a person receiving steroids for GVHD, or who received GCV at < 100 days post-BMT).	GCV 5 mg/kg/dose i.v. q 12 h x 7 days followed by 5 mg/kg/day i.v. on 5 days/week x 2 weeks **[BIII]**.	

HSV	Prevention of HSV reactivation in HSV seropositive BMT recipients. Start Acyclovir at the beginning of conditioning therapy and continue until engraftment or until mucositis resolves (approximately 30 days post-BMT in allogeneic BMT recipients).	Acyclovir. For children < 35 kg., give 4 mg/kg p.o. b.i.d. or 250 mg/m^2/dose i.v. q 12 h **[BIII]**.	Acyclovir 1000 mg/24h p.o. ÷ 3-5 times/day or 80 mg/kg/d in 3-4 divided doses p.o. q.d.. Maximum oral dose is 80 mg/kg/day for children. Note: 1. For patients requiring prophylaxis for both CMV and HSV post-engraftment, Ganciclovir (GCV) alone provides effective prophylaxis for both CMV and HSV. 2. Valacyclovir is not approved for use in children.
VZV	Prevention of VZV disease in BMT recipients following VZV exposure in VZV seronegative BMT recipients who are < 24 months post-BMT, or are ≥24 months post-BMT and on immunosuppressive therapy or have chronic GVHD). Give within 96 hours (preferably 48 h) after close contact with a person with either chickenpox or shingles.	VZIG 125 U/10 kg. (22 lbs.) of body weight given I.M., up to a maximum dose of 625 U or 5 vials **[AII]**.	(See *Immunization* section.)

Influenza	Prevention of influenza A and B in BMT recipients.	Lifelong annual seasonal influenza vaccination during the influenza season pre-BMT and resuming ≥6 months post-BMT **[BIII]**. Dose and type of influenza vaccine vary by child's age: Age / Dose / Vaccine 6 - 35 mo. 0.25 ml split virus 3-8 years 0.5 ml split virus 9-12 years 0.5 ml split virus > 12 years 0.5 ml whole or split virus	Note: Children <9 years of age receiving influenza vaccination for the first time require two doses of vaccine spaced at least one month apart. See *Immunization* section.
	Prophylaxis and pre-emptive treatment of influenza A in BMT recipients during nosocomial or community influenza A outbreak settings.	Rimantadine: For children 1 - 9 years of age: 5 mg/kg/d p.o. ÷ q.d. or b.i.d. **[CIII]**. Maximum daily dose = 150 mg. For children ≥ 10 years of age (<40 kg): 5 mg/kg/d p.o. ÷ q.d. or b.i.d. Children ≥ 10 years of age (≥ 40 kg): 200 mg po qd or bid.	Amantadine Dose: For children 1-9 years of age: 4.4 - 8.8 mg/kg/day. For children 9-12 years of age: 100 mg p.o. b.i.d. Maximum daily dose = 200 mg Note: Neither Rimantadine nor Amantadine should be given to children < 1 year of age.

Respiratory Syncytial Virus (RSV)	Prophylaxis for RSV lower respiratory infection (LRI) in hypogammaglobulin-emic BMT recipients.	RSV-IVIG. May be given in place of IVIG during RSV season for pediatric BMT recipients who are on routine IVIG therapy (1), (e.g., those with hypogammaglobulin-emia) **[CIII]**. RSV season in the United States is usually Nov.- April. Usual RSV-IVIG dose is 750 mg/kg per month i.v., or a 1 mg/1 mg dosing substitution of RSV-IVIG for IVIG may be used for patients who normally require high IVIG doses to maintain serum IgG > 400 mg/dl. May administer more frequently than monthly as needed to keep serum IgG > 400 mg/dl.	None. Note: RSV-IVIG is contraindicated in patients with IgA deficiency, who may have allergic reactions or anaphylaxis when receiving blood products containing IgA **[DIII]**.
	Pre-emptive treatment of RSV URI or early LRI in pediatric BMT recipients	Aerosolized Ribavirin (1) 6 g/300 cc sterile water to make a concentration of 20 mg/ml. Give 18 h/day x 10 days in a tent **[CIII]**. For BMT recipients with LRI who cannot tolerate a tent, or who have RSV URI, may give Ribavirin as 2 g over 2 h q 8 h via face mask x 10 days. Use small particle aerosol generator model SPAG-2.	

Bacterial infections	Prevention of bacterial infections in allogeneic BMT recipients with severe hypogammaglobulinemia (serum IgG level < 400 mg/dl) within the first 100 days post-BMT.	Intravenous immune globulin (IVIG) 400 mg/kg/month. May increase dose and/or dose frequency as needed to keep serum IgG levels > 400 mg/dl **[CIII]**. OR Some BMT experts use an IVIG dose of 125 mg/kg/wk (500 mg/kg/month. If serum IgG levels remain <400 mg/dl, dose may be raised to 250 mg/kg/week.	None. NOTE: 1. IVIG is contraindicated in patients with anti-IgA antibodies **[DIII]**. 2. Some experts recommend checking serum IgG levels q 2 weeks in patients receiving IVIG replacement therapy. 3. See *Bacterial Infections* section footnote for information on how to obtain IVIG.
Streptococcus pneumoniae	Prevention of pneumococcal disease in BMT recipients.	23-valent pneumococcal polysaccharide vaccine at 12 and 24 months post-BMT **[BIII]**.	Note: 1. 23-valent pneumococcal polysaccharide vaccine should not be given to children < 2 years of age due to lack of efficacy **[DI]**. 2. The prevalence of penicillin-resistant *S. pneumoniae* is increasing in the United States. 3. See *Immunization* section.
Haemophilus influenzae type b	Prevention of invasive *Haemophilus influenzae* type b (Hib) disease in BMT recipients. Prophylaxis of invasive Hib disease in BMT recipients who are exposed to persons with *H. influenzae* type b disease (1).	*Haemophilus influenzae* type b conjugate vaccine. Give to all BMT recipients at 12, 14, and 24 months post-BMT **[BII]**. Rifampin 0-1 mo old: 10 mg/kg/dose p.o. q.d. x 4 days, > 1 mo old: 20mg/kg/day p.o. q.d. x 4 days. Maximum dose: 600 mg/day **[BIII]**	None None See *Immunization* section.

Methicillin-resistant *Staphylococcus aureus* (MRSA)	Elimination of MRSA carrier state to prevent MRSA disease in chronic carriers.	Mupirocin calcium ointment 2%. Using a cotton-tip applicator or equivalent, apply to nares bid x 5 days, or to wounds qd x 2 weeks. Note: Safety in children < 12 years of age has not been established.	Bacitracin is considered safe for use in children. If used, it used like mupirocin, but no standardized protocol has been properly evaluated.
Candida spp.	Prophylaxis for fluconazole-susceptible *Candida* spp. during neutropenia in allogeneic BMT recipients. Administer Fluconazole from the day of transplantation (day 0) until engraftment (approximately 30 days post-BMT), or until 7 days after the ANC > 1,000 cells/mm^3.	Fluconazole: For children 6 months - 13 years of age, give Fluconazole 3-6 mg/kg/day p.o. or i.v.**[AI]**. Maximum dose 600 mg/day. For children > 13 years of age, give Fluconazole, 400 mg. p.o. or i.v. q.d. **[AI]**.	None
Pneumocystis carinii	Prophylaxis of *Pneumocystis carinii* pneumonia (PCP) in: 1. all allogeneic BMT recipients, and 2. autologous BMT recipients with underlying hematologic malignancies such as lymphoma or leukemia, for those receiving intense conditioning regimens or graft manipulation, or for those who have recently received fludarabine or 2-chlorodeoxyadenosine (2-CDA) (3). Give PCP prophylaxis from the time from engraftment for at least 6 months post-BMT. Continue beyond 6 months post-BMT for the *duration of immunosuppression for all persons who* 1) are receiving immunosuppressive therapy (e.g. prednisone or cyclosporine) or who 2) have chronic GVHD.	Trimethoprim-Sulfamethoxazole (TMP-SMZ), Dose: 150 mg TMP/750 mg SMZ/m^2/d in 2 divided doses p.o. t.i.w. on consecutive days **[AII]**. OR Single dose p.o. t.i.w. on consecutive days, or 2 divided doses p.o. q.d. x 7 days or 2 divided doses p.o. t.i.w. on alternate days. Some experts recommend giving PCP prophylaxis for 1-2 weeks prior to BMT (day -14 to day - 2) **[CIII]**.	1. Dapsone (for BMT recipients ≥ 1 month of age), 2 mg/kg (max 100 mg) p.o. q.d. **[BIII]**. OR 2. IV pentamidine 4 mg/kg q 2-4 weeks, OR aerosolized pentamidine (for BMT recipients children ≥ 5 years of age) 300 mg q month via Respirgard II ™ nebulizer **[CIII]** Note: 1. TMP-SMZ is not recommended for patients < 2 months of age due to risk of kernicterus, 2. Patients who are receiving sulfadiazine-pyramethamine for toxoplasmosis therapy are protected against PCP and do not need additional PCP prophylaxis.

Toxoplasma gondii	Prophylaxis of *T. gondii* disease in *T. gondii* seropositive allogeneic BMT recipients. Start after engraftment and give as long as patients remain on immunosuppressive therapy (generally until 6 months post-BMT).	Trimethoprim-Sulfamethoxazole (TMP-SMZ), Dose: 150 mg TMP/750 mg SMZ/m^2/d in 2 divided doses p.o. t.i.w. on consecutive days **[AII]**. OR Single dose p.o. t.i.w. on consecutive days, or 2 divided doses p.o. q.d. x 7 days or 2 divided doses p.o. t.i.w. on alternate days.	For those who are intolerant to TMP-SMZ, the following drugs can be substituted: Clindamycin 20-30 mg/kg/d in 4 divided doses p.o. q.d. *plus* pyramethamine 1 mg/kg p.o. q.d. *plus* leucovorin 5 mg p.o. q 3 days **[CIII]**. Note: 1. TMP-SMZ is not recommended for patients < 2 months of age due to risk of kernicterus, 2. In allogeneic BMT recipients, clinical toxoplasmosis has occurred despite the use of TMP-SMZ for PCP prophylaxis (5).

Strongyloides spp.	Prevention of strongyloidiasis hyperinfection in 1. BMT candidates whose pre-BMT screening tests are positive for *Strongyloides* spp., and 2. in all BMT candidates with an unexplained eosinophilia and a compelling travel or residence history suggestive of exposure to *Strongyloides stercoralis.* Medication should be given before BMT.	Ivermectin 200 μg/kg p.o. q.d. x 2 consecutive days (6,7). 1 tablet = 6 mg. Body Weight (kg) — Oral Dose < 15 — Not recommended ≥ 15 - 24 — ½ tablet 25-35 — 1 tablet 36-50 — 1½ tablets 51-65 — 2 tablets 66-79 — 2½ tablets ≥80 — 200 μg/kg (Note: In immunocompromised persons, multiple courses at two week intervals may be required. However, cure may not be achievable. Safety and efficacy of Ivermectin has not been established during pregnancy.)	Thiabendazole 50 mg/kg/day ÷ b.i.d. x 2 days, maximum dose = 3 g/24 h. (Note: Thiabendazole is contraindicated during pregnancy.)

Traveler's diarrhea	For prophylaxis in BMT recipients who remain immunocompromised and are traveling in developing countries.	Trimethoprim-Sulfamethoxazole (TMP-SMZ), 150 mg TMP/750 mg SMZ/m^2/d in 2 divided doses p.o. t.i.w. on consecutive days **[CIII]**. If used, may administer for duration of stay.	Single dose p.o. t.i.w. on consecutive days. Note: 1. TMP-SMZ is not recommended for patients < 2 months of age due to risk of kernicterus, 2. Resistance to TMP-SMZ is common in tropical areas, 3. Usual doses of TMP-SMZ for PCP prophylaxis should provide some protection against traveler's diarrhea. 3. is not recommended for use in children. WARNING: **Use of aspirin-containing products including Bismuth subsalicylate is contraindicated in persons < 18 years of age** unless prescribed by a physician because they have been associated with Reye syndrome (11).

Mycobacteria tuberculosis (TB)	Prevention of TB in 1. highly immunocompromised BMT recipients or candidates who have been exposed to someone with active, infectious (e.g., sputum smear positive) pulmonary or laryngeal tuberculosis, regardless of the BMT recipient's or candidate's TST status, and 2. to BMT recipients or candidates with a positive TST and who were not previously treated and have no evidence of active TB disease.	Isoniazid (INH) 10-20 mg/kg/day p.o. or i.m. (maximum dose 300 mg/day) X 9 months (for at least 270 doses) (1,8,9), AND Pyridoxine (Vitamin B_6) Dose: 1-2 mg/kg/day p.o. q.d. The dose required may vary depending on age and condition (10). Give Pyridoxine to nutritionally deficient BMT recipients and candidates while on INH-PT to reduce the occurrence of INH-induced neuropathy **[BIII]**.	1. A twice weekly (b.i.w.) schedule of INH may be considered before BMT **[CIII]**. The biweekly INH dose is 15 mg/kg p.o. or i.m. b.i.w. 2. A 2 month pyrazinamide/rifampin (PZA/RIF) preventive therapy (PT) regimen may be considered in BMT candidates who are not at risk for serious rifampin drug interactions and whose BMT is not scheduled until at least 2 weeks after the 2 month course of PZA/RIF is completed (8,9) **[CIII]**. The usual PZA dose is 15-30 mg/kg/day po (maximum daily PZA dose = 2 g) OR 50-70 mg/kg per dose p.o. b.i.w. (maximum PZA dose is 3.5 g). The usual RIF dose is 10 mg/kg/day or 10 mg/kg/dose given b.i.w. (Maximum RIF dose is 600 mg.) 3. Routine use of a two month PZA/RIF PT regimen is not recommended after BMT due to the risk of serious rifampin drug interactions **[DIII]**, 4. Persons who are latently infected with a rifamycin and isoniazid drug-resistant TB should be placed on PT regimens that involve at least two anti-TB drugs to which the infecting strain is susceptible (8) **[BIII]**, and 5. For persons who are intolerant to INH, consultation with a TB expert should be sought.

Drug Dosing Chart References

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Glossary of Acronyms

AAP - American Academy of Pediatrics
ABMTR - Autologous Blood and Marrow Transplant Registry
ACIP - Advisory Committee on Immunization Practices
ACP - American College of Physicians
ACV - acyclovir
ANC - absolute neutrophil count

BCG - Bacillus of Calmette and Guérin
BMT - bone marrow transplant. For these guidelines, this term includes all hematopoietic cell transplants from both blood and marrow.
bid - twice a day

CDC - Centers for Disease Control and Prevention
CMV - cytomegalovirus
CMVIG - cytomegalovirus immune globulin
CRV - community respiratory virus

DPT - diphtheria, pertussis, tetanus vaccine
DT - diphtheria, tetanus vaccine

EBV - Epstein-Barr virus
EBV-VCA - Epstein-Barr virus - viral capsid antigen
EPA - Environmental Protection Agency
FDA - Food and Drug Administration

G-CSF - Granulocyte colony-stimulating factor
GCV - ganciclovir
GM-CSF - Granulocyte-macrophage colony-stimulating factor
GVHD - graft-versus-host disease

HBIG - hepatitis B immune globulin
HCFA - Health Care Financing Administration
HCWs - health care workers Hep B - hepatitis B vaccine
HEPA filter - high efficiency particulate air filters
Hib - *Haemophilus influenzae* type b
HICPAC - Hospital Infection Control Practices Advisory Committee
HIV - human immunodeficiency virus
HRIG - Human rabies immune globulin
HRSA - Health Research Services Administration
HSV - *Herpes simplex* virus

IPV - inactivated polio vaccine
IBMTR - International Bone Marrow Transplant Registry
IDSA - Infectious Disease Society of America IMIG - intramuscular immune globulin
IM - intramuscular
IV - intravenous
IVIG or IGIV - intravenous immune globulin

LAF - laminar air flow
LD - legionnaire's disease
LRI - lower respiratory infection

MMR - measles, mumps, rubella vaccine
MRSA - methicillin resistant *Staphylococcus aureus*
NCHSTP - National Center for HIV, STD, and TB prevention, CDC
NCID - National Center for Infectious Disease, CDC
NHLBI - National Heart, Lung, and Blood Institute at NIH
NIH - National Institutes of Health
NIP - National Immunization Program, CDC
NMDP - National Marrow Donor Program
OPV - oral polio vaccine

PCR - polymerase chain reaction
po - by mouth
PT-LPD - post-transplant lymphoproliferative disorder
PZA/RIF - pyrazinamide/rifampin

q - every
qd - every day
qod - every other day
qid - four times a day

RSV - respiratory syncytial virus
RSVIG - respiratory syncytial virus immune globulin
STD - sexually transmitted disease

TIG - tetanus immune globulin
tid - three times a day
tiw - three times a week
TB - *Mycobacteria tuberculosis*
Td - Tetanus-diphtheria vaccine
TIG - tetanus immune globulin
TMP-SMZ - Trimethoprim - sulfamethasaxole
TST - tuberculin skin test
TU - Tuberculin Units

UCB - umbilical cord blood
USDA - United States Department of Agriculture
URI - upper respiratory infection
VISA - Vancomycin-intermediate *Staphylococcus aureus*
VZIG - *Varicella zoster* immune globulin
VZV - *Varicella zoster* virus

Definitions

acute GVHD - a form of GVHD which usually occurs within the first 40 days post-BMT, and presents as skin, gastrointestinal, and liver injury. It is graded on a scale of I-IV. Grade I is defined as mild and Grades II-IV are defined as moderate to severe.

allogeneic BMT - BMT in which the donor is not the BMT recipients.

autologous BMT - BMT in which the donor is also the BMT recipient

bone marrow transplantation - For this document, includes all hematopoietic stem cell transplants, regardless of source of cells (bone marrow, peripheral or umbilical cord blood).

chronic GVHD - A form of GVHD which occurs during Phases II and III post-BMT in some allogeneic BMT recipients. In contrast to acute GVHD, chronic GVHD is graded as either limited or extensive chronic GVHD. Chronic GVHD presents similarly to autoimmune, connective-tissue disorders such as scleroderma or systemic lupus erythematosus and is associated with cellular and humoral immunodeficiencies, including macrophage deficiency, impaired neutrophil chemotaxis, poor response to immunization, and severe mucositis. Recovery from chronic GVHD may take weeks, months, or years.

day 0 - the day of transplant.

empiric treatment - Antimicrobial agents are administered to a subgroup of patients with clinical disease who 1) lack either clear diagnosis, or 2) diagnosed illness lacks definitive therapy. This is done to in an attempt to prevent severe disease or death.

engraftment - for both adults and children, it is defined as the point at which a BMT recipient can maintain a sustained absolute neutrophil count (ANC) of $>500/mm^3$ and sustained platelet count of 20,000 - 50,000/mm^3 lasting at least 3 consecutive days without transfusions; in unrelated allogeneic BMT recipients, engraftment occurs at a median of 22 days post-BMT (range 6-84 days).

graft-versus-host disease (GVHD) - a condition which occurs allogeneic BMT recipients when the transplanted cells recognize the recipient's cells as non-self and attack them. GVHD primarily occurs in allogeneic BMT recipients, particularly those receiving matched, unrelated donor transplants, although autologous or syngeneic BMT recipients may occasionally develop a mild, self-limited form of GVHD. GVHD is a major risk factor for infection. GVHD is further classified as acute *vs*. chronic GVHD.

immunocompetent BMT recipients - BMT recipients who are $\geq$24 months post-BMT, are not on immunosuppressive therapy, and do not have graft-versus-host disease (GVHD).

immunosuppressed BMT recipients - BMT recipients who are < 24 months post-BMT, or are on immunosuppressive therapy, or have graft-versus-host disease (GVHD).

neutropenia - ANC < 500/mm^3

Phase I - pre-engraftment phase, 0 - < 30 days post-BMT
Phase II - post-engraftment phase, 30-100 days post-BMT
Phase III - Late phase > 100 days post-BMT

pre-emptive treatment - Antimicrobial agents are administered to a subgroup of patients prior to the appearance of clinical disease. Pre-emptive therapy is predicated on the use of a laboratory marker or patient characteristic that identifies those at highest risk of serious disease when antimicrobial intervention would be effective in aborting the disease process and preventing severe disease or death.

prophylaxis - antimicrobial agents are administered to all persons in a population to prevention a common and important infections.

syngeneic BMT - BMT donor is HLA-identical sibling

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